Sex differences in the management and outcomes of stroke

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Supervisors

Doctor Seana Gall

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Declaration of Originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by any other person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human experimentation, and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

The research using the pooling data from 13 population-based studies forming the INternational STroke oUtCome sTudy (INSTRUCT; Chapters 2-6) was approved by the Tasmanian Health and Medical Human Research Ethics Committee; reference number is H0014861. All of the participating studies had signed informed consent and approval from their respective local Ethics Committees.

The research using the data from the Australian Stroke Clinical Registry (AuSCR; Chapters 7-10) was approved by the Tasmanian Health and Medical Human Research Ethics Committee; reference number is H0015287. My research proposal was also approved by the AuSCR Research Task Group and its Management Committee in August 2016. Appropriate ethics and/or governance approvals were obtained for all participating hospitals in AuSCR and the Australian Institute of Health and Welfare to conduct data linkage to the National Death Index.

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Statement of Authority of Access and Regarding Published Work

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Statement of Co-Authorship

This thesis includes work which has been published, submitted, or ready for publication in peer-reviewed journals. Publication/manuscript details for each Chapter are described in the "Publications arising from the thesis" section.

The following people and institutions contributed to the publication of work undertaken as part of this thesis:

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Located in Chapter 3

Candidate Phan was the primary author. Candidate contributed 70% to the study concept and design, acquisition, analysis and interpretation of data, literature review, and drafting of the manuscript.

Dr. Blizzard, Dr. Reeves, Dr. Thrift, Dr. Cadilhac, Dr. Sturm, Dr. Heeley, Mr. Otahal contributed to the study concept and design, interpretation of data, and critical revision of manuscript for intellectual content.

Dr. Vemmos, Dr. Anderson, Dr. Parmar, Dr. Krishnamurthi, Dr. Barker-Collo, Dr. Feigin, Dr. Bejot, Dr. Cabral, Dr. Carolei, Dr. Sacco, Dr. Chausson, Dr. Olindo, Dr. Rothwell, Dr. Silva, Dr. Correia, Dr. Magalhães, Dr. Appelros, Dr. Kõrv, Dr. Vibo, Dr. Minelli contributed to the study concept and design, interpretation of data, and revision of manuscript for intellectual content.

Dr Gall contributed to the study concept and design, supervision of the study, acquisition, interpretation of data, and critical revision of manuscript for intellectual content.

Paper 2: **Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): A Meta-Analysis of Individual Participant Data**

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Paper 3: **Sex differences in long-term health-related quality of life after stroke in the INternational STroke oUtComes sTudy (INSTRUCT)**

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Dr Gall contributed to the study concept and design, supervision of the study, acquisition, interpretation of data, and critical revision of manuscript for intellectual content.

Paper 4: **Sex differences in severity of stroke in the INternational STRoke oUtComes sTudy (INSTRUCT): a meta-analysis of individual participant data**

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Candidate Phan was the primary author. Candidate contributed 70% to the study concept and design, acquisition, analysis and interpretation of data, literature review, and drafting of the manuscript.

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Dr Gall contributed to the study concept and design, supervision of the study, acquisition, interpretation of data, and critical revision of manuscript for intellectual content.

Paper 5: **Sex differences in care and long-term mortality after stroke: Australian Stroke Clinical Registry (AuSCR)**

Located in Chapter 8

Candidate Phan was the primary author. Candidate contributed 70% to the study concept and design, acquisition, analysis and interpretation of data, literature review, and drafting of the manuscript.

Dr. Blizzard, Dr. Lannin, Dr. Thrift, Dr. Anderson, Dr. Kim, Dr. Grimley, Dr. Castley, Dr. Hand contributed to the study concept and design, interpretation of data, and critical revision of manuscript for intellectual content.

Dr. Gall and Dr. Cadilhac contributed to the study concept and design, supervision of the study, acquisition, interpretation of data, and critical revision of manuscript for intellectual content.

Paper 6: **Sex differences in specific-cause mortality and excess death rates after stroke: the Australian Stroke Clinical Registry**

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Candidate Phan was the primary author. Candidate contributed 70% to the study concept and design, acquisition, analysis and interpretation of data, literature review, and drafting of the manuscript (60%).

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Dr. Gall and Dr. Cadilhac contributed to the study concept and design, supervision of the study, acquisition, interpretation of data, and critical revision of manuscript for intellectual content.

Paper 7: **Sex differences in health-related quality of life at 3-6 months after stroke: Australian Stroke Clinical Registry**

Located in Chapter 10

Candidate Phan was the primary author. Candidate contributed 70% to the study concept and design, acquisition, analysis and interpretation of data, literature review, and drafting of the manuscript.

Dr. Blizzard, Dr. Lannin, Dr. Thrift, Dr. Anderson, Dr. Kim, Dr. Grimley, Dr. Castley, Dr. Hand contributed to the study concept and design, interpretation of data, and critical revision of manuscript for intellectual content.

Dr. Gall and Dr. Cadilhac contributed to the study concept and design, supervision of the study, acquisition, interpretation of data, and critical revision of manuscript for intellectual content.

We, the undersigned agree with the above stated contributions for each of the above published (or submitted) peer reviewed manuscripts contained within this thesis:

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Thesis Abstract

Background: Women appear to experience worse outcomes after stroke than men but the causes of these differences have not been conclusively determined. There is also some evidence that women receive evidence-based stroke care less often than men but how this influences outcomes after stroke is unclear. There is a need for high-quality studies to explore these sex differences to inform interventions to address these differences.

Aims: My aims were to 1) quantify the sex differences in management and outcomes of stroke; and 2) to identify factors that contribute to the worse outcomes in women.

Methods: Two different data sources were used in the thesis. The first was individual participant data (IPD) on long-term outcomes after stroke from 13 population-based stroke incidence studies conducted in Europe, Australasia, South America, and the Caribbean between 1987 and 2014, forming the INternational STroke oUtCome sTtudy (INSTRUCT). Data on sociodemographics, stroke-related factors, pre-stroke health, stroke management, and post-stroke factors were obtained. Study outcomes were: (1) severity of acute stroke, (2) long-term all-cause mortality, (3) functional outcomes and participation restriction, and (4) HRQoL up to 5 years after stroke. I performed IPD meta-analyses of the sex differences in these outcomes (at 1 and 5 years after stroke) and contributing factors, forming the first four studies of the thesis.

The second dataset included first-ever strokes admitted to 39 hospitals between 2010 and 2014 in the Australian Stroke Clinical Registry (AuSCR) - a national stroke registry. The AuSCR incorporates standardised methods of data collection for

important processes of stroke care in Australia and patient outcomes. Study factors included sociodemographics, stroke-related factors, evidence-based processes received in hospital (i.e. stroke unit care, thrombolysis, secondary prevention medications), and self-reported 3-month indicators (e.g. living arrangements). Study outcomes were (1) all-cause mortality, (2) causes of death (COD) up to 1 year after stroke, and (3) HRQoL at 3-6 months follow-up. The causes of the sex differences in stroke care and outcomes were investigated using the AuSCR, forming the other three studies as part of the thesis.

Results: In the meta-analyses of 16,957 strokes included in the INSTRUCT, women were about 35% more likely to be deceased and 32% more likely to have a poor functional outcome by 1 year after stroke compared to men. Women also had greater participation restriction and poorer HRQoL than men.

The sex differences in stroke outcomes were mostly explained by women's greater age, greater pre-stroke functional limitations and more severe strokes than men. The presence of atrial fibrillation (AF) also accounted for the greater mortality in women and post-stroke depression contributed to the sex differences in HRQoL. There was limited evidence that stroke management, socioeconomic status, cardiovascular risk factors, or other comorbidities were responsible for the worse outcomes in women compared to men. Similar results were observed in 5-year analyses. Further examination of stroke severity at the acute stage showed that pre-stroke factors only partly explained why women presented with more severe strokes compared to men.

In the analyses of the AuSCR on 14,118 strokes, women had a 40% greater all-cause mortality at 1 year following stroke. The COD differed between sexes with women having more deaths attributed to stroke or other cardiovascular diseases (CVD; e.g. AF and heart failure) than men. Women's lower aspirin administration within 48 hours of admission, advanced age and stroke severity explained the greater all- and specific-cause mortality. About 60% of the participants (n=6852) had HRQoL assessments at 3-6 months. Women had worse HRQoL than men, with the difference mostly explained by age, stroke severity, and 3-month place of residence (aged care). However, older women had poorer HRQoL than older men, independent of the measured covariates including evidence-based care and other factors.

Conclusions: Women faced poorer outcomes after stroke than men. Worse outcomes in women were mostly because of pre-stroke factors including age but also stroke severity, pre-stroke functional limitations and, to a lesser extent, AF. Of all aspects of management examined, only lower aspirin administration in women contributed to their greater mortality. The findings highlight the importance of better management of vascular risk factors and comorbidity in the elderly, with more women prevalent in that age group than men. The findings suggest opportunities for interventions to reduce sex differences in stroke outcome may include better access to evidence-based care for cardiovascular and general health, and opportunities for post-stroke rehabilitation, especially targeting those with less capacity to recover (i.e. pre-stroke functional limitation, more severe strokes and mood disorders). Further research on the potential biological origin of sex differences in stroke severity may also be warranted.

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List of Publications

Publications arising from this thesis:

Phan H, Blizzard L, Thrift A, Cadilhac D, Sturm J, Heeley E, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Reeves M, Otahal P, Gall S. Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy). *Circ Cardiovasc Qual Outcomes*. 2017; 10. https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.116.003436. (Journal IF ~ 4.5; citation: 14). *This article was highlighted in the special edition 'Spotlight: Women and Heart Disease' of the Circulation: Cardiovascular Quality and Outcomes aligned with Go Red for Women® campaign by American Heart Association, which recognises that the burden of cardiovascular diseases in women is a major concern worldwide. This paper is accompanied by an editorial noting its novelty, significance and implications for improving long-term outcome after stroke* (*see Editorial by Lisabeth and Madsen at* https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.117.003546)

Phan HT, Blizzard CL, Thrift AG, Cadilhac D, Sturm J, Heeley E, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Reeves M, Otahal P, Gall S. Factors contributing to sex differences in functional outcomes and participation after stroke. *Neurology*. 2018. https://doi.org/10.1212/WNL.0000000000005602. (Journal IF ~ 8.3; citation: 2). This paper was also accompanied by an editorial noting its novelty, significance and implications for improving long-term outcome after stroke. (*see Editorial by Andrew and Srikanth at* https://doi.org/10.1212/WNL.0000000000005591)

Draft or submitted manuscripts arising from this thesis:

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Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, Otahal P, Rothwell P, Bejot Y, Cabral NL, Appelros P, Kõrv J, Vibo R, Minelli C, Gall SL. Sex differences in severity of stroke in the INternational STRoke oUtComes sTudy (INSTRUCT): a meta-analysis of individual participant data. *At the time of submission of this thesis, the contents of this manuscript (in Chapter 6) have been under review following request for revisions from the Journal of American Heart Association.*

Phan HT, Gall SL, Blizzard CL, Lannin N, Thrift AG, Anderson CS, Kim J, Grimley R, Castley HC, Hand P, Cadilhac D. Differences in stroke care and outcomes after stroke for women compared to men: Australian Stroke Clinical Registry (AuSCR). Sex differences in care and long-term mortality after stroke: Australian Stroke Clinical Registry (AuSCR). *At the time of submission of this manuscript (in Chapter 8), the contents of this chapter have been under review following request for revisions from the Journal of Women's Health.*

Phan HT, Gall SL, Blizzard CL, Lannin N, Thrift AG, Anderson CS, Kim J, Grimley R, Castley HC, Hand P, Cadilhac D. Sex differences in specific-cause mortality and excess death rates after stroke: the Australian Stroke Clinical Registry. *At the time of submission of this thesis, the contents of this manuscript (in Chapter 10) have been circulated to co-authors in preparation for submission for publication.*

Manuscripts published during candidature, but external to thesis material:

Vo TXH, Cao NHT, **Phan TKH**, Nguyen TTM, Tran VT, To HL, Truong HTA, Phan TH. Prevalence of hypertension and diabetes among adults in Ho Chi Minh City – a community-based study in an urban district. *Vietnam Journal of Preventive Medicine Vietnam*. 2017; 27.8 (ISSN: 0868 - 2836)

Gall S, **Phan H**, Madsen T, Reeves M, Rist P, Jiménez M, Lichtman J, Dong L, Lisabeth L. A focused update of sex differences in patient reported outcome measures (PROMs) after stroke. *Stroke*. 2018; 49(3):STROKEAHA.117.018417. (Journal IF ~ 6; citation: 5).

Published abstracts

1. **P T Kim Hoang,** L Blizzard, T Pham, V Srikanth, S Gall. Health related of quality of life of stroke care-givers of stroke patients in Viet Nam. *Int J Stroke.* 2014;9(Suppl 1):27–48.

2. Gall S, **Phan HT**, Blizzard L, Thrift A, Cadilhac D, Heeley E, Sturm J, Reeves M, INSTRUCT Study Investigators. Trends in Long-term Case-mortality After Stroke From the International Stroke Outcomes Study (INSTRUCT): An Individual Participant Data Meta-analysis of Incident Strokes. *Stroke.* 2016;47(Suppl 1):A89.

3. **Phan HT**, Reeves MJ, Blizzard L, Thrift A, Cadilhac D, Heeley E, Sturm J, INSTRUCT Study Investigators. Sex Differences in Long-term Mortality and Disability After Stroke: The International Stroke Outcomes Study. *Stroke.* 2016;47(Suppl 1):AWMP53.

4. **Phan HT**, Reeves MJ, Blizzard L, Thrift A, Cadilhac D, Heeley E, Sturm J. Sex Differences in Long-term Mortality and Disability After Stroke: The International Stroke Outcomes Study. *Cerebrovasc Dis.* 2016;41(Suppl 1):O002.

5. **Phan H**, Blizzard L, Thrift A, Cadilhac D, Sturm J, Konstantinos V, Anderson C, Feigin V, Bejot Y, Cabral N, Carolei A, Olindo S, Rothwell P, Correia M, Appelros P, Vibo R, Minelli C, Reeves M, Gall S, INSTRUCT study group. Sex differences in health-related quality of life (HRQoL) in the long-term after stroke: The INternational STroke OUtComes Study. *European Stroke Journal* 2016;(Suppl 1)1:286.

6. Reeves M, Gall S, **Phan Kim H**, Blizzard L, Thrift A, Cadilhac D, Sturm J, Anderson C, Konstantinos V, Feigin V, Bejot Y, Cabral N, Carolei A, Olindo S, Rothwell P, Correia M, Appelros P, Vibo R, Minelli C. Sex differences ischemic stroke severity (NIHSS): The INternational STroke OUtComes STudy (INSTRUCT). *European Stroke Journal* 2016;(Suppl 1)1:285.

7. **Phan H**, Blizzard L, Thrift A, Cadilhac D, Sturm J, Heeley E, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Reeves M, Otahal P, Gall S. Sex differences in health-related quality of life (HRQoL) in the long-term after stroke: The INternational STroke OUtComes STudy (INSTRUCT). *Cerebrovasc Dis* 2016;42(Suppl 1):P187.

8. **Phan H**, Blizzard L, Thrift A, Cadilhac D, Sturm J, Heeley E, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Reeves M, Otahal P, Gall S. Sex Differences in Long-term Mortality and Disability After Stroke: The International Stroke Outcomes Study. *Cerebrovasc Dis* 2016;42(Suppl 1):O18.

9. Pham T, Blizzard L, **Phan H**, Vo H, Srikanth V, Thrift A, Nguyen L, Nguyen T, Gall S. Long Term Outcomes of First-Ever Stroke in HoChiMinh City, Vietnam. *Cerebrovasc Dis* 2016;42(Suppl 1):1–157

10. **Phan HT**, Blizzard L, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, Heeley E, Feigin V, Parmar P, Krishnamurthi R, Barker-Collo S, Parag V, Konstantinos V, Anderson C, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Otahal P, Gall S. Differences Between Men and Women in Long-term Participation Restriction After Stroke: The International Stroke Outcomes Study (INSTRUCT). *Stroke*. 2017;48(Suppl 1):ATP171.

11. **Phan HT**, Cadilhac D, Thrift AG, Blizzard L, Anderson C, Kim J, Gall S. Differences in Stroke Management do not Account for the Greater Long-term Mortality After Stroke in Women Compared to Men: Australian Stroke Clinical Registry (AuSCR). *Stroke*. 2017;48(Suppl 1):ATP171.

12. Gall SL, **Phan HT**, Cadilhac D, Blizzard L, Thrift AG, Anderson C, Kim J, Lannin N. Women and stroke poorer quality of life at 3-6 months after stroke in women compared to men is due to age and severity but not clinical care. *European Stroke Journal*. 2017;1(Suppl 1)2:66.

13. **Phan HT**, Blizzard L, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, Heeley E, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Otahal P, Gall S. Sex differences in the management of stroke: The INternational STroke OUtComes STudy (INSTRUCT). World Congress on Public Health, April 2017, Melbourne, Australia (Oral presentation).

14. Pham T, Blizzard L, **Phan H**, Srikanth V, Thrift A, Nguyen L, Nguyen T. Poor outcomes among female patients with stroke at 3 months in Viet Nam. World Congress on Public Health, April 2017, Melbourne, Australia (Oral presentation).

15. **Phan HT**, Cadilhac D, Blizzard L, Lannin N, Thrift AG, Anderson C, Kim J, Grimley R, Gall SL. Differences in stroke care and outcomes after stroke for

women compared to men: Australian Stroke Clinical Registry (AuSCR). *European Stroke Journal.* 2017;12(Suppl 3).

16. Gall S, **Phan HT**, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, Heeley E, Otahal P Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C. Sex differences in survival, functional outcomes and health-related quality of life are mostly due to women's greater age, more severe stroke and pre-stroke health compared to men: the INternational STRoke oUtComes sTudy (INSTRUCT). *European Stroke Journal.* 2017;12(Suppl 3).

17. Gall S, **Phan HT**, Reeves MJ, Bushnell C. A systematic review of the sex differences in the use of emergency services following stroke. *European Stroke Journal.* 2017;12(Suppl 3).

18. **Phan HT**, Gall SL, Blizzard L, Lannin NA, Thrift AG, Anderson C, Kim J, Cadilhac DA. Lower Health-Related Quality of Life (HRQoL) At 3-6 Months After Stroke in Both Women and Men Compared to Those Without Stroke: An Observational Study From The Australian Stroke Clinical Registry (AuSCR). *Stroke*. 2018;49(Suppl 1):ATP175.

19. **Phan HT**, Gall SL, Blizzard CL, Lannin NA, Thrift AG, Anderson CS, Kim J, Grimley R, Castley HC, Cadilhac DA. Sex difference in specific-cause mortality after stroke: the Australian Stroke Clinical Registry. *European Stroke Journal* 2018;3(suppl 1):AS15-020.

Scientific presentations

Presentations at international conferences

- World Stroke Congress, 2018, Canada (Oral & poster presentations)
- World Congress on Public Health, 2017, Australia (Oral presentations)
- International Stroke Conference 2017, USA (Oral & poster presentations)
- European Stroke Conference 2016, Italia (Oral presentation)
- European Stroke Organisation Conference 2016, Spain (Poster presentation)
- Asia Pacific Stroke Conference 2016, Australia (Oral & moderated poster presentations)

Presentations at domestic conferences

- The 11th Graduate Research Conference, 2017, UTAS (Oral presentation)
- The 10th Graduate Research Conference, 2016, UTAS (Oral & poster presentations)
- Menzies Student Showcase, Research week, 2016, UTAS (Poster presentation)
- The 4th Tasmanian Health Science Higher Degree Research (HDR) Student Conference 2016, UTAS (Oral & poster presentations)
- Menzies Student Showcase, Research week, 2015, UTAS (Poster presentation)
- The 9th Graduate Research Conference, 2015, UTAS (Poster presentation)

- Australian Society for Medical Research (ASMR) Medical Research Week 2017 – Tasmanian Postgraduate Student Awards, 2017, UTAS (Oral presentation)

Invited presentation

- Ho Chi Minh City Stroke Conference, 2017, Vietnam (‘Sex difference in management and outcomes of stroke’)

Awards Resulting from the Thesis

- Menzies's Ten of the Best Award 2018 for the paper published in the Circulation Cardiovascular Quality and Outcome
- New Investigator Award Finalist 2017 — Stroke Society of Australasia
- The Winner of Three Minute Thesis (3MT) Competition – heats, Medical Science Precinct, University of Tasmania, Hobart, Tasmania, 2017
- Three Minute Thesis (3MT) Grand Final Competition Finalists – Graduate Research Conference, University of Tasmania, Hobart, Tasmania, 2017. https://www.youtube.com/watch?v=Tt-WgQyLk0I&feature=youtu.be
- To be selected as one of 12 mentees of the 2017 L'Oréal Australian For Women in Science mentoring program (July 2017 – January 2018; mentor: Associate Professor Deanna D'Alessandro from the University of Sydney)
- Tasmanian Postgraduate Student Research Awards Finalist – Australian Society for Medical Research (ASMR) Medical Research Week, Hobart, 2017. My oral presentation was selected as the final six out of 42 candidates.
- People's choice Award - Three Minute Thesis (3MT) Competition – Graduate Research Conference, University of Tasmania, Hobart, Tasmania, 2016. https://www.youtube.com/watch?v=_td3I4fiaUs

- Most outstanding oral presentation Award - Tasmanian Health Science Higher Degree Research (HDR) Student Conference, 2016.
- Stroke Society of Australasia Bursary Award for highly ranked abstract – Asia Pacific Stroke Conference combined with the 27th Stroke Society of Australasia Scientific Meeting, 2016.
- The Young Investigator Award for highly ranked abstract – European Stroke Conference, Venice, Italia, 2016.
- Merle Weaver Postgraduate Scholarship to undertake the PhD study on stroke at Menzies Institute for Medical Research – University of Tasmania, 2015-2018.
- ***An offer to receive a 2018 Endeavour Research Fellowship*** by Australian Government Department of Education and Training. Only 698 recipients have been offered a 2018 Endeavour scholarship or fellowship all over the world.
- ***Travel Award*** from Ho Chi Minh City Stroke Association Conference, 2017, Vietnam to attend and give an invited presentation at the Ho Chi Minh City Stroke Conference, 2017.
- ***Travel Award for Junior Investigators*** for highly ranked abstract – International Stroke Conference, Houston, Texas, USA, 2017.
- ***Travel Award*** from Tasmania Student Union and the Network of Women Students Australia (NOWSA) to attend the NOWSA Conference, Canberra, 2017
- ***Travel grant*** from Menzies Institute for Medical Research - Research Enhancement Program - Stimulating National and International Collaborations

(obtained by Dr Seana Gall) to do analyses at Monash University with the project 'Sex difference in stroke management and outcome in Australia Stroke Clinical Registry' forming part of my PhD thesis, Melbourne, April and December 2017.

- ***Travel Grant Award*** for highly ranked abstract – European Stroke Organisation Conference, Barcelona, Spain, 2016.

Other awards/grants

- ***Research grant*** (CIA) for project 'Mortality and health-related of quality of life of stroke patients at two years after stroke in Viet Nam' – Pham Ngoc Thach University of Medicine, Vietnam, 2015.
- ***Research grant*** (CIC) for project "Prevalence of hypertension and diabetes among adults in Ho Chi Minh City using WHO STEPWISE approach to surveillance (STEPS) method – a community in an urban district" from the Community Health Development Institute – Vietnam, 2015-2018.

Research Activities and Community Engagement

- Deliver a oral presentation at the Open day – University of Tasmania, 2016, Hobart, Australia
- Deliver a oral presentation the Annual Postgraduate Students' Evening– The Royal Society of Tasmania, 2016, Hobart, Australia
- Deliver a community talk at University of the Third Age (U3A) – Hobart (October 2017)
- Interview with the Mercury newspaper on publication in Circulation: Cardiovascular Quality and Outcomes (03 March 2017)
- Moderator of a seminar about ‘Leadership for Women in STEMM’ by Dr Meredith Nash at Menzies Institute for Medical Research (June, 2017)
- Running the workshop ‘Stroke and women’s challenges’ to raise women’s awareness of stroke for women in the Network of Women Students Australia (NOWSA) Conference, Canberra (July 2017)
- Interview with the ABC Radio Hobart on my PhD research and Three minute thesis presentation at Graduate Research Conference (07 September 2017)
- Co-chair of the Student Committee 2018 – Menzies Institute for Medical Research

List of Abbreviation

ADL	Activities of daily living
AER	Absolute excess death rate
AF	Atrial fibrillation
AIHW	Australian Institute of Health and Welfare
AQoL	Assessment of Quality of Life
AuSCR	Australian Stroke Clinical Registry
BI	Barthel Index
BMI	Body mass index
CFR	Case fatality rate
CHD	Coronary heart disease
CI	Confidence interval
COD	Cause of death
CT scan	Computed tomography scan
CVD	Cardiovascular disease
ECG	Electrocardiogram
EQ-5D	European Quality of Life – 5 dimensions
GCS	Glasgow Coma Scale
GHQ-28	General Health Questionnaire-28
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICF	International Classification of Functioning Disability and Health

ICH	Intracerebral haemorrhage
ICIDH	International Classification of Impairments, Disability and Handicap
IDA	Irritability, Depression and Anxiety Scale
IHD	Ischaemic heart disease
INSTRUCT	INternational STRoke oUtCome STudy
IPD	Individual participant data
IS	Ischaemic stroke
LHS	London Handicap Scale
LOC	Loss of consciousness
MADRS	Montgomery–Åsberg Depression Rating Scale
MCID	Minimal clinically important difference
MRI	Magnetic resonance imaging
MRR	Mortality rate ratio
mRS	The modified Rankin Scale
NEMESIS	North East Melbourne Stroke Incidence Study
NHMRC	National Health and Medical Research Council
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
PR	Prevalence ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International PROSPEective Register Of systematic reviews
PSD	Post-stroke depression

PVD	Peripheral vascular disease
RR	Relative risk
r-tPA	Recombinant tissue plasminogen activator
SAH	Subarachnoid haemorrhage
SD	Standard deviation
SEP	Socioeconomic Position
SF36	Short Form-36 items
sHR	Specific hazard ratio
SMR	Standardised mortality ratio
SSS	Scandinavian Neurological Stroke Scale
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UNSS	Unified Neurological Stroke Scale
UTAS	University of Tasmania
WHO	World Health Organization

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Thesis Aims, Hypothesis, and Guide to Chapters

Aims

The aims of the thesis were to:

1) quantify the sex differences in stroke management and outcomes following stroke;

2) to identify factors that contribute to the worse outcomes in women compared to men.

Hypotheses

1. Women with stroke receive evidence-based care less often than men. Age and pre-stroke factors such as cardiovascular risk factors will mostly account for these differences.
2. In unadjusted analyses, women, compared to men, will have higher mortality, worse functional outcomes, greater participation restriction, and poorer HRQoL in the long term after stroke.
3. Age, stroke severity and co-morbid disease will account for most of the sex differences in these long-term outcomes after stroke. Others confounders such as clinical management and post-stroke mental health will partially account for the sex differences in long-term outcomes.

Thesis organisation and guide to chapters

The thesis provides a comprehensive examination of the differences between men and women in stroke outcomes including all-cause and specific-cause mortality,

functional outcome, participation restriction, health-related quality of life, in-hospital management, and stroke severity.

Two different datasets were used in the thesis: one is a data pooling study including 13 population-based stroke incidence studies worldwide that met the 'gold standard' criteria for such studies, and the other was from a national stroke registry including data collected from 39 hospitals around Australia with up-to-date information on quality of care and outcomes. Therefore, the methods for each dataset are presented in two separate chapters. The structure of the thesis is as follows:

Chapter 1: Review of literature

I summarise key topics related to thesis including what is known about sex differences in patient outcomes after first-ever stroke, limitations of current research, the measurement of outcomes following stroke, and factors that may contribute to sex difference in outcomes after stroke.

Chapter 2: Methods for the International Stroke Outcome Study (INSTRUCT) using pooling data of population-based stroke incidence studies

In this chapter, I provide a systematic search for eligible studies for the individual participant data (IPD) meta-analysis of high-quality stroke incidence studies forming the INSTRUCT. I also present general information on the methods used in the INSTRUCT (Chapter 3-6). More detailed information on covariates, outcomes and data analysis are included in the relevant results chapters.

Chapter 3: Sex difference in long-term mortality after stroke in the INSTRUCT

I report estimates of sex differences in mortality at 1 and 5 years after stroke from the meta-analysis of IPD in INSTRUCT including examination of confounding factors of the sex difference are presented in this chapter.

Chapter 4: Sex difference in long-term functional outcome and participation after stroke in the INSTRUCT

I report estimates of sex difference in functional outcome and participation restriction up to 5 years after stroke from 11 out of 13 studies included in INSTRUCT.

Chapter 5: Sex difference in long-term health-related quality of life (HRQoL) in the INSTRUCT

I report estimates of sex difference in HRQoL at 1 and 5 years after stroke from 10 out of 13 high quality stroke incidence studies included in INSTRUCT.

Chapter 6: Sex difference in severity of stroke in the INSTRUCT

In this chapter, I report sex difference in severity of stroke using National Institute Health Stroke Scale from a meta-analysis of individual participant data from 8 out of 13 studies included in INSTRUCT.

Chapter 7: Methods related to Australian Stroke Clinical Registry (AuSCR) data collection and application in my research

The chapter describes the methods for the studies using the AuSCR – a national stroke registry (Chapters 8-10). More detailed information on covariates, outcomes and data analysis are included in the relevant results chapters.

Chapter 8: Sex difference in management and all-cause mortality after stroke in the AuSCR

In this chapter, I report sex difference in management of acute stroke and mortality up to 1 year after stroke using AuSCR data between 2010 and 2014.

Chapter 9: Sex difference in specific-cause mortality and excess death rates after stroke: the AuSCR

I report sex difference in causes of death after stroke, including excess death rates after stroke compared to the general population, up to 1 year after stroke using a subset of AuSCR data between 2010 and 2013 in this chapter.

Chapter 10: Sex difference in HRQoL after stroke in the AuSCR

In this chapter, I report sex difference in HRQoL at 3-6 months after stroke using AuSCR data between 2010 and 2014.

Chapter 11: Summary, implications and future directions

This chapter draws together the major findings and conclusions, summaries the contributions of the thesis to the field, and provides recommendations for future research.

Appendices: A-I

This chapter provides supplementary information for the thesis. Some tables and figures that were published as peer-reviewed supplemental materials have been added to the Methods sections (Chapters 2 and 7) for easier interpretation.

Chapter 1: Review of literature

1.1 Impact of stroke

Stroke affects 33 million people, including 16.9 million first-ever strokes, each year worldwide.[1] In 2013, stroke was responsible for 6.5 million of deaths, accounting for 11.8% of total deaths worldwide.[2] It was also a leading cause of long-term disability.[3] Despite a substantial decline in stroke mortality rates over the last few decades,[2] the absolute number of stroke deaths and disability-adjusted life-years (DALYs) lost are rising.[1,4] One-third of 5-year survivors remain dependent on others,[5] and up to a half experience psychosocial comorbidity (mainly depression) after stroke.[6] There is a considerable proportion of stroke survivors with poor health-related quality of life up to 5 years after stroke.[7]

In Australia, stroke was the third leading cause of death in 2013.[2] It was estimated that approximately 440,000 Australians were living with the effects of stroke in 2014,[8] and this number is anticipated to surge to over 700,000 by 2032.[9] Stroke was responsible for 4.5% of the overall of burden of disease in Australia[10] with the total financial costs estimated to be $5 billion in 2012.[8] Approximately two-thirds of those living with stroke suffered a disability that meant they required assistance to do activities of daily living.[8]

The global burden of stroke is predicted to continue to grow in association with an ageing population.[2] Therefore, stroke remains a serious public health concern with devastating physical, psychological (emotional and mental), and economic impacts on

not only patients but also their families,[11] communities, and the health-care system.[12-14]

1.2 Sex differences in the epidemiology of stroke

It is not often recognised that stroke has placed a higher burden on women than men. Globally, women have a higher crude incidence of stroke than men but this is reversed once age is taken into account.[7,15] Although stroke mortality has decreased over the past two decades,[16,17] the annual crude death rate from stroke in women (94.8 per 100,000 people) has outweighed that of men (80.3 per 100,000 people).[18] The global burden of stroke in women is predicted to continue to grow[19] associated with an increase in life expectancy for both sexes.[15] (**Figure 1-1**). Because women live longer than men,[20] women that suffer stroke may be exposed to more physical disabilities, psychological and social problems, and have fewer years of healthy life compared to men.[21]

In Australia, stroke was ranked as the third leading contributor of death for women in comparison with being ranked fifth for men, accounting for 6.1% and 3.9% of the total burden of disease, respectively.[10] The crude death rate of stroke was approximately 50% greater in women than in men (45.6 vs 26.6 per 100,000)[22] and disabilities appeared to be disproportionately higher amongst women survivors.[8]

Among studies of outcomes after stroke, women appeared to have poorer functional outcomes, greater handicap, and worse health-related quality of life than men both in the short[23] and long term.[24]

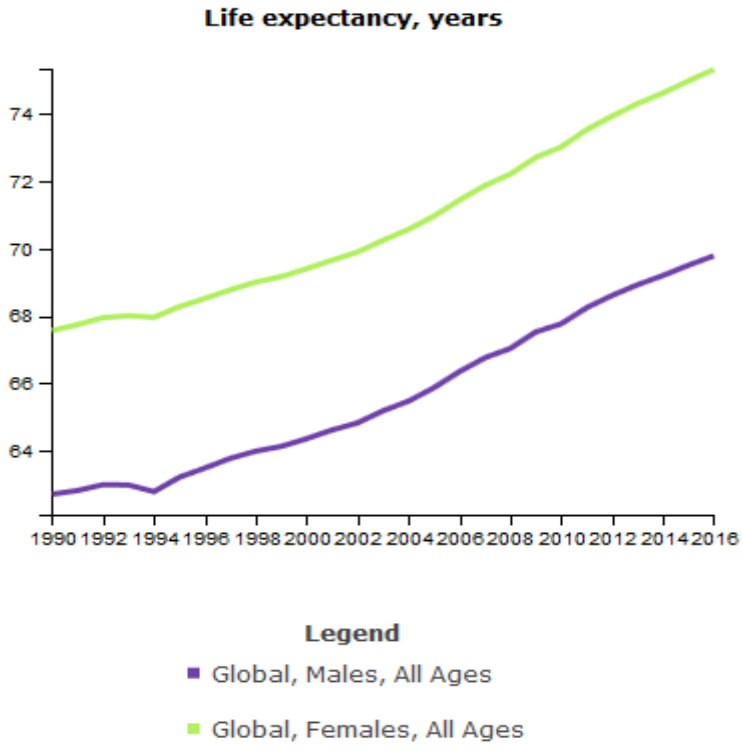


Figure 1-1. Global life expectancy by sex. The table was created using data from the Global Burden of Disease Study 2015.[25] (Online data: http://ghdx.healthdata.org/gbd-results-tool)

1.3 Limitations of existing studies of sex differences in outcomes

There is an increased interest related to investigating the differences between men and women in outcomes after stroke. However, uncertainty exists over the sex differences due to several limitations of the existing research into the long term following stroke (≥1 year), identified in a review led by Gall et al (2012).[24] More recently, our focused update of sex differences in patient outcomes ≤ 1 year after stroke less than one year (Gall et al. 2018) has again identified similar problems to the aforementioned issues of the long-term studies.[23]

Overall, the studies of the sex differences in stroke outcome have mainly been reported in the short-term up to 6 months. Many studies have been based on hospital cohorts or convenience samples. This is a potential problem because the selection bias from the hospital-based studies may adversely affect the conclusion of the sex differences in outcomes.[26] On the one hand, those with more severe strokes may be more likely to be admitted to hospital and have poorer survival and disability than those not admitted to hospital with less severe stroke.[27] Therefore, selection bias from the hospital-based studies may inflate the sex differences in outcomes after stroke.[28] On the other hand, women are less often admitted to hospital potentially due to more often residing in an institution when they experience their stroke,[29] which may bias hospital-based outcome studies of sex differences in outcomes in an unpredictable way.[26]

Population-based stroke incidence studies, therefore, provide better external and internal validity and are ideally designed to explore sex differences in outcomes after stroke.[30] The highest quality are those that have adhered to standardised guidelines for 'ideal' stroke incidence studies (**Table 1-1**) as proposed by Sudlow and Warlow,[31] and by Malmgren et al.[32] These guidelines are discussed in detail below.

Although there are many good quality studies of stroke outcome, very few studies have been specifically designed to examine the aetiology of sex differences in outcomes. Most of the existing studies either failed to undertake detailed analyses of sex differences[5,33-52] or potential confounding factors were not well examined.[53,54] The associations between sex and outcomes after stroke have usually been reported as incidental findings in multivariable models (e.g. using step-wise regression) with

considerable variation in outcome measurement and adjustment for covariates.[24] The role of potential confounding or mediating variables for sex disparities are still inconclusive. This is because very few investigators have examined the relative effects of individual covariates and provided both unadjusted and adjusted results to see the influence on effect estimates. Additionally, in some studies the focus on the sex difference has only included ischaemic stroke, which accounts for 75-80% of events, instead of all stroke types.[55] In other studies, only one aspect of outcomes in the long term after stroke, such as survival, has been examined.[41,56]

Table 1-1. Core criteria for a comparable study of stroke incidence proposed by Sudlow and Warlow[31] and by Malmgren et al.[32]

Standard definitions
World Health Organization definition
First-ever-in-a-lifetime stroke
Standard methods
Complete, community-based case ascertainment, based on multiple overlapping sources
Prospective study design, ideally with "hot pursuit" of cases
Large, well-defined, stable population
Reliable method for estimating denominator
Standard data presentation
Whole years of data
Not >5 years of data averaged together
Men and women presented separately
Include ages up to ≥85 years if possible
Standard mid-decade age bands (e.g., 55 to 64 years) used in publications
Unpublished 5-year age bands available for comparison with other studies
Presentation of 95% confidence intervals around incidence rates

1.4 Study designs to examine the sex differences in outcomes

Population-based stroke incidence studies offer better external and internal validity than other studies undertaken within hospital settings or where a convenience sample has been used.[30] These high-quality studies provide the best way to document the processes of care, stroke outcomes (e.g. case fatality, functional outcome, and HRQoL), and costs of stroke on representative cohorts of people that have had a stroke.[31] As these studies are conducted prospectively, important stroke-related factors can be collected such as pathological subtypes, socio-demographics, stroke severity, and comorbidities that are often unavailable in routinely gathered data from other sources.

'Gold standard' population-based stroke incidence studies are ideal to examine the sex differences in outcomes after stroke. However, it is cumbersome and labour-intensive to conduct these high-quality studies, which can partly explain why a large number of them were conducted a long time ago (i.e. 1970s-1990s).[57] These studies, therefore, may be less able to provide information on contemporary stroke care. In addition, there are some countries where population-based stroke incidence studies cannot be conducted nor repeated due to costs and labour intensity.[58] Further, examination of longer term outcomes means that by the time follow-up assessments are completed, the care provided at baseline some years later may be outdated.

National stroke registries allow us to capture aspects of the quality of care through measuring current processes of in-hospital care as well as associated outcomes after stroke.[25] These clinical registries, therefore, could be served as a proxy for

population-based incidence studies in locations where the majority of incidence cases are treated in hospital.[58] There are several national quality registries for stroke (e.g. the Get-with-the-Guidelines-Stroke program in the United States,[59] the Australian Stroke Clinical Registry in Australia,[60] or the Riks-Stroke register in Sweden),[61] which provide up-to-date data on stroke performance indicators aligned with evidence-based practice recommendations. The national registries include standardised data collection to ensure data quality and often have adequate power to test research hypotheses among different subgroups of patients. Nevertheless, detailed information on pre-existing comorbidities and some patient outcomes (e.g. post-stroke depression) may not be captured in these registries.

1.5 Measurement of outcomes after stroke

Patient outcomes after stroke can be gathered from the studies of stroke, either based on community-based or hospital samples. Outcomes that are commonly assessed in research include survival, functional outcomes, participation restriction, and health-related quality of life. An overview of these outcomes is described below.

1.5.1.1 Survival

Mortality rate (or death rate) is calculated by diving number of deaths occurring in the population during the stated period of time by the number of persons at risk of dying during the period often expressed as a rate per year.

Mortality can be collected nationally for comparison across countries such as through national data linkage of death registers among the whole population. However, the

accuracy of official stroke-mortality statistics depends not only on the coding methodology but also on the quality of the data itself which may misclassify stroke.[62,63]

Mortality after stroke can also be gathered. In these studies, survival can be expressed as a ***case fatality rate*** (CFR). The CFR represents a measure of risk of deaths due to stroke within a designated population of stroke "cases" and usually expressed as a percentage.

Survival is also reported in stroke studies, indicating the percentage of people who are alive after a stroke event in a specific time of follow-up after diagnosis.

1.5.1.2 Functional outcome and participation restriction (or handicap)

The World Health Organization (WHO) first introduced a detailed concept of impairment, disability, and handicap in manual of International Classification of Impairments, Disabilities and Handicap (ICIDH)[64] in 1980. ***Impairment*** refers to any loss or abnormality of psychological, physiological or anatomical structure or function. ***Disability*** is a functional limitation with regard to a particular activity or task in the range considered normal for an individual. ***Handicap*** is defined as a disadvantage in filling a role in life for a given individual.

Changes in health care during the 20th century called for a shift from the treatment focus of acute disease to the management of chronic disease and/or disability, in other words, “from disease to health”. To avoid the negative connotations of certain terms used previously by the original ICIDH, the development of the ICIDH-2[65] by the

WHO (1998) provided the terms "***activities***" instead of disability and "***participation***" instead of handicap. The ICIDH-2 covers the same three dimensions: (1) body structures or functions; (2) personal activities; and (3) participation in society with adding contextual factors (environmental and personal). The WHO (2001) provided the new model, namely International Classification of Functioning, Disability and Health (ICF),[66] comprising components of ***functioning*** and disability "in the context of health".

The terminology '***functional outcome***' (or activity limitation, or disability) used in this thesis is based on the ICF classification.[66] Having worse functional outcomes after stroke means the patients are restricted in the activities of daily living (ADL),[66] and may require supported care.[67]

Participation restriction (or handicap) reflects the influence of functional loss on a person's social, economic and recreational activities after stroke.[24] Participation restriction is rarely measured in stroke outcomes research, although it is a person-centred outcome that is important to survivors of stroke[68] and can greatly affect stroke survivor's health-related quality of life.[69] In the thesis, the official terminology '***participation restriction***' based on the ICF[66] definition was used instead of the term 'handicap'. Handicap is defined as a disadvantage in filling a role in life for a given individual.[65] To avoid the negative connotations of the traditional term, 'participation restriction' is widely accepted by both medical and non-medical clinicians and increasingly used in stroke research.[68,70]

1.5.1.3 Health-related quality of life

Health-related quality of life (HRQOL) is a multi-dimensional concept that has evolved since the 1980s that encompasses domains related to functional ability, psychological state, social function, and an individual's perception of his or her health.[71,72] HRQoL is defined as an assessment of how the individual's well-being may be affected over time by a health condition such as disease, disability, or disorder.[73] HRQOL has become an important component of health surveillance and is generally considered a valid indicator of service needs and intervention outcomes. It goes beyond direct measures of population health, life expectancy and causes of death, and focuses on the impact of health status on quality of life. There are a number of HRQoL measurements[74] including generic HRQL and condition-specific HRQoL instruments. Generic instruments are designed to be able to compare HRQOL across populations or different diseases while condition-specific instruments are designed to assess HRQOL with questions and scales that are specific to a disease or condition. Given the rising burden of stroke worldwide, HRQoL is an important outcome to measure as it reflects the person's experience. Generic and stroke specific measurements of HRQoL are widely used in stroke research with acknowledged strengths and limitations.[75]

Changes in scores of patient-reported outcomes including HRQoL should be assessed in the context of clinically or minimally meaningful differences. These can also be used to evaluate the effectiveness of an intervention as well as improve healthcare decisions and policies.[76] The minimal important difference or minimal clinically important difference (MCID) is considered as a standard approach in the

interpretation of clinical relevance of changes in patient-reported outcomes.[76] The MCID represents the smallest change in a treatment outcome that an individual patient would identify as important and which would warrant a change in the patient's management.[77] There are various computational techniques to assess the meaningful threshold for HRQoL utility scores such as distribution-based and anchor-based (e.g. regression, average change approach, minimum detectable change approach, change difference approach and ROC curves) methods.[78] However, interpreting the results of studies reporting HRQoL is not straightforward. The MCID has not been commonly reported in the studies designed to examine the sex difference in HRQoL after stroke.

1.6 Magnitude of the sex differences in outcomes in existing research

Current reviews have been undertaken to explore the sex differences in stroke worldwide, which generally have shown less favourable outcomes in physical, psychological and HRQoL after stroke in women when compared to men.[23,79-84] In the following sections, I present some selected findings of the sex differences in outcomes following stroke identified in the current literature. Women are frequently under-represented in stroke randomised controlled trials (RCTs), potentially leading to selection bias that may affect analyses of differences between men and women in the receipt of stroke care and outcomes after stroke.[85] I have, therefore, included population-based or hospital-based studies in the chapter.

1.6.1 Survival outcome

As explained earlier, at the population level, women appear to have greater mortality than men based on the data from the Global Burden of Disease Study 2015 (**Figure 1-2**).[25] However, the quality and completeness of the global mortality data may be sometimes questionable because of potential data coding problems of underlying causes of death from the national death registrations.[86]

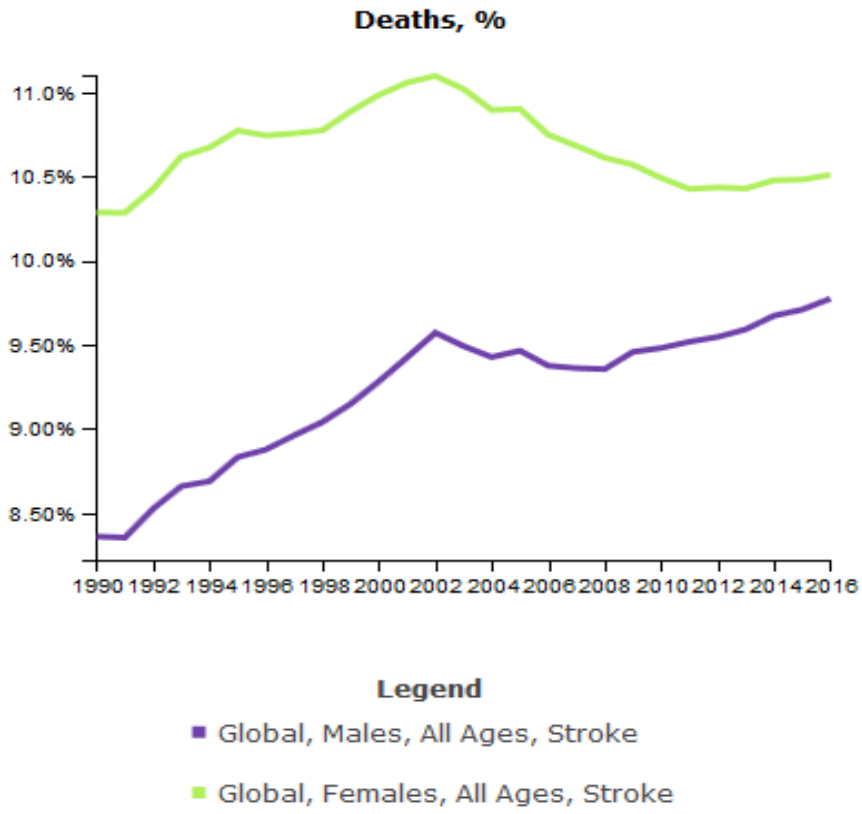


Figure 1-2. Global stroke mortality by sex. The table was created using data from the Global Burden of Disease Study 2015[25] (Online data: http://ghdx.healthdata.org/gbd-results-tool)

Table 1-2 presented my general overview of selected studies with survival outcome data following stroke. Women generally have lower survival after stroke both in the short and long term although the magnitude of the differences varied between studies varies (**Table 1-2**). In a meta-analysis of 31 high-quality population-based stroke incidence studies conducted between 1970 and 2004 it was found that women had about 25% greater 28-day CFR of stroke than men.[56] There are some other studies whereby the CFRs for women and men have been discordant (e.g. at 1 month,[87,88] or up to 6 years after stroke; **Table 1-2**).[39,89] There is some evidence that women and men differ in respect to important risk factors of stroke,[82] which may contribute to the sex differences in survival after stroke. However, current research is limited by the lack of detail on potential contributing factors to explain the sex differences.

Among the few studies with multivariable adjustment (**Table 1-2**), women appeared to have greater mortality compared to men in unadjusted analyses (e.g. relative risk: 1.34-1.38 up to 3 months, or hazard ratio: 1.18 up to 5 years after stroke).[90] However, these sex differences in survival were mostly explained by contributing factors including age, stroke severity, stroke type, and co-morbid disease. After accounting for the covariates, the mortality was lower for women compared to men in four studies (1 month,[91] 1 year,[92] 5 years,[90] and 10 years[93]) while no evidence of the sex differences was observed in the remaining studies (1 month,[92,94,95] 1 year,[96] and 5 years[97]).

There have been a myriad of discrepancies in study design (i.e. hospital-based or population-based), setting and analysis method (i.e. using Cox model, Poisson regression), and adjustment for covariates between studies. Few studies examined

whether differences in management after stroke influenced the sex difference in survival. This suggests a need for studies designed to comprehensively examine factors contributing to the sex differences in mortality, particularly in the long term after stroke.

Table 1-2. Summary of selected studies with survival outcome data by sex up to 10 years after stroke

							Poor outcome in adjusted results			
Year	**Author**	**Design**	**Time**	**Measure**	**Unadjusted results**	**Adjusted results**	**Women < Men**	**Women = Men**	**Women > Men**	**Adjustments**
2014	Stranjalis[88]	MC PB Prosp	1 mth	Case fatality	M:F 22.4% vs 19.6%					
2012	Pikija[87]	SC PB Prosp	1 mth	Case fatality	M:F 23.4% vs 23.6%					
2012	Wang[95]*	SC PB Prosp	1 mth	Mortality		F:M **'92-'98** RR 1.3 (95% CI 0.6-2.6) **'99-'05** RR 0.6 (95% CI 0.3-1.1) **'06-'12** RR 1.0 (95% CI 0.6-1.8)		x		Age
2011	Walker[89]	SC PB Prosp	3-6 yrs	Case fatality	M:F 46.5% vs 44.3%					

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Poor outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
2010	Gall[94]*	SC PB Prosp	1 mth	Mortality	F:M RR 1.36 (95% CI 1.08-1.71)	F:M RR 1.25 (95% CI 0.90-1.73)		x		Age, pre-stroke health, stroke severity and use of anticoagulants at discharge
2009	Chausson[39]	SC PB Prosp	5 yrs	Case fatality	M:F 42.5% vs 56.3%					
2009	Palnum[91]*	MC PB Prosp	3 mths	Mortality	F:M **1-mth** RR 1.34 (95% CI 1.26- 1.44) **3-mth** RR 1.38 (1.30-1.46)	F:M **1-mth** RR 0.79 (0.72- 0.86) **3-mth** RR 0.81 (0.75- 0.87)	x			Patient characteristics, department, and fulfillment of quality of care criteria
2009	Vaartjes[97]*	MC HB Prosp	1 mth	Mortality	F:M case fatality 26.6% vs 28.7%	F:M HR 1.13 (95% CI 1.08–1.19)			x	Age
			1 yr		34.6% vs	HR 1.09 (1.04–1.14)			x	
			5 yrs		37.3%	HR 1.00 (0.96–1.03)		x		

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Poor outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
					51.5% vs 54.6%					
2009	Oh[90]*	MC HB Prosp	5 yrs	Mortality	F:M case fatality **1-mth:** 4.3% vs 3.2% **3-mth:** 7.0% vs 5.4% **1-yr:** 12.2% vs 9.9% **5-yr:** 25.3% vs 22.6%					Age, stroke Hx, stroke severity, potential cardioembolic stroke, smoking, co-morbid CVD, tPA, time delays from onset to hospital arrival
					5-yr F:M HR 1.18 (95% CI 1.10–1.27)	**5-yr** F:M HR 0.85 (95% CI 0.79–0.93)	x			
2005	Anderson[93]*	SC PB Prosp	10 yrs	Survival	M: F survival **1-yr** 70.3% vs 66.7%, ns **5-yr** 40.0% vs 38.9%, ns	F:M **1 yr** HR 1.47 (95% CI 1.10-2.00)	x			Age, stroke severity, stroke type, health behaviour, co-morbid CVD

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Poor outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
					10-yr 17.4% vs 18.7%, ns	**5-yr** HR 1.47 (1.23-1.76) **10-yr** HR 1.49 (1.28-1.76)				
2003	Appelros[96]	SC PB Prosp	1 yr	Case fatality	M:F HR 0.7 (95% CI 0.5-0.9)	M:F HR (ns)		x		Age, co-morbid CVD, severity, place of residence TIA, pre-stroke dementia, smoking
2000	Holroyd-Leduc[92]*	MC HB Prosp	1 mth	Mortality		F:M OR 0.96 (95% CI 0.91- 1.01)		x		Age, and comorbid conditions
			1 yr			OR 0.94 (0.90-0.98)	x			

*denotes studies designed to examine the sex differences in outcome
SC: single centre, MC: multi-centre, HB: hospital-based, PB: population-based, prosp: prospective study, Hx: history, tPA: Tissue plasminogen activator, mths: months, yr: year, M: men; W: women; CVD: cardiovascular disease; RR: relative risk; HR: hazard ratio; ns: non-significant

1.6.2 Functional outcome

Women generally have worse functional outcomes than men in both short and long term studies after stroke.[23,24] However, there are variations in outcome measures (e.g. modified Rankin Scale − mRS, Barthel Index − BI, and disability on Katz ADL items), study settings (population-based or hospital-based), definition of poorer outcome (e.g. BI< 95, BI≤60, or mRS≥3) between these studies that hamper comparisons.

The existing reviews highlight the fact that very few studies were population-based and specifically designed to examine the aetiology of sex differences in functional outcomes.[23,24] Only four out of 21 long-term studies (≥ 1 year after stroke) were aimed to investigate the sex differences and none of these four studies were population-based.[24] Similarly, of the 22 studies with functional outcome up to 1 year after stroke, only 3 were population-based studies that were designed to examine sex differences.

According to the most recent review, among studies that designed to examine the sex differences up to 1 year after stroke,[23] women had 44-61% lower odds of good functional outcome or 29-62% greater odds of poor functional outcome in unadjusted analyses (**Table 1-3**). Adjustment of covariates, most commonly age, stroke severity, comorbidities, and pre-stroke function reduced the association by 9-20% but did not fully explain the sex differences among 6/8 studies (female:male adjusted odds ratios [OR] of good outcome: 0.37-0.75; OR of poor outcome: 1.17-1.74). The list of covariates in study-specific multivariable models and magnitude of the sex differences substantially differed between studies. Few studies examined whether

differences in management after stroke influenced the sex difference in functional outcome. More comprehensive research designed to quantify the sex differences in functional outcomes in the long term after stroke and identify the contributing factors is needed.

1.6.3 Participation restriction

Women generally faced a higher crude risk of having participation restriction in both the short and the long term after stroke.[23,24] In adjusted analyses, the sex differences were mostly explained by age, post-stroke disability and depression. It is noticeable that participation restriction is rarely measured in stroke outcomes research.[24] Also very few investigators have provided unadjusted and adjusted effect estimates of the sex differences (**Table 1-4**).[23] Participation was assessed by different instruments (i.e. London Handicap Scale, the Work and Social Adjustment Scale and the participation of the Stroke Impact Scale) that are not comparable between studies. Uncertainty also exists over the contributing factors to the sex differences in participation restriction. Few studies examined whether differences in management after stroke influenced the sex difference in participation restriction. There is a need for further research designed to examine the differences between men and women in participation restriction following stroke and identify the contributing factors to the differences.

Table 1-3. Summary of sex differences in functional outcome up to 1 year after stroke in studies designed to examine sex difference with multivariable adjustment (source: Gall et al., 2018)[23]

Year	Author	Design	Time	Outcome measure	Unadjusted results	Adjusted results	Worse outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
2014	Wu[98]	SC HB Prosp	6 mths	BI≥95	W:M OR 0.47 (95% CI 0.26, 0.74)	W:M OR 0.37 (95% CI 0.19, 0.87)			x	Age, race, stroke type, co-morbidities, severity
2013	Koton[99]	MC HB Prosp	90 days	BI≤60	W:M OR 1.62 (95% CI 1.22, 2.16)	W:M OR 1.41 (95% CI 0.99, 2.01)		x		Age, marital status, pre-stroke modified Rankin scale (mRS), severity, stroke history (Hx)
2011	Yesilot[100]	SC HB Prosp	DC	mRS≥3		M:W OR 1.46 (95% CI 1.04, 2.06)			x	Age, pre-stroke disability, TACS, nasogastric tube/urinary catheter, motor symptoms, atrial fibrillation (AF)
2010	Kim[101]	SC HB Prosp	90 days	mRS≥3		M:W OR 1.59 (95% CI 1.02, 2.49)			x	Age, stroke severity, small vessel occlusion, stroke Hx, co-morbidities

Year	Author	Design	Time	Outcome measure	Unadjusted results	Adjusted results	Worse outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
			1 yr	mRS≥3		M:W OR 1.74 (95% CI 1.01, 2.99)			x	Age, stroke severity, small vessel occlusion, stroke Hx, co-morbidities
2009	Petrea[67]	PB	3-6 mths	Disability on Katz ADL items		W:M ORs Eating 1.05 Dressing 1.79 Grooming 1.64 Transfer 2.37* Walking 1.91		x		Age, systolic blood pressure, hypertension treatment, AF, smoking, co-morbid cardiovascular disease, diabetes mellitus, pre-stroke Katz ADL
2008	Gargano[102]	MC HB Prosp	DC	Ordinal mRS	W:M OR 1.29 (95% CI 1.12, 1.49)	W:M OR 1.17 (95% CI 1.01, 1.35)			x	Age, pre-stroke ambulatory status
2008	Reid[103]	SC HB Prosp	DC	BI≥95	W:M OR 0.61 (95% CI 0.51, 0.74)	W:M OR 0.75 (95% CI 0.61, 0.94)			x	Age, pre-stroke functional status, stroke type, stroke severity, AF

Year	Author	Design	Time	Outcome measure	Unadjusted results	Adjusted results	Worse outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
2007	Gargano[104]	HB Prosp	90 days	BI≥95	W:M OR 0.44 (95% CI 0.26, 0.74)	W:M OR 0.37 (95% CI 0.19, 0.87)			x	Age, race, pre-stroke ambulatory status, pre-stroke, discharge mRS, proxy, stroke Hx

ADL: activities of daily living; AF: atrial fibrillation; SC: single centre, MC: multi-centre, HB: hospital-based, PB: population-based, prosp: prospective study, BI: Barthel Index, mths: months, yr: year; M: men; W: women

Table 1-4. Summary of sex differences in participation restriction up to 1 year after stroke in studies with multivariable adjustment (source: Gall et al., 2018)[23]

							Worse outcome in adjusted results			
Year	**Author**	**Design**	**Time**	**Measure**	**Unadjusted results**	**Adjusted results**	**Women < Men**	**Women = Men**	**Women > Men**	**Adjustments**
2014	Vincent[105]*	SC HB Prosp	1, 3, 6, 9 and 12 mths	LHS	NR	1 mth, p=0.78 3 mths p=0.55 6 mths p=0.96 9 mths p=0.64 12 mths p=0.39		x		None
2014	Ghosal[106]	PB	12 mths	Social Participation SIS	NR	NR		x		Education, cardiac problems, thalamic lesion, tea consumption, neurological history
2012	Jalayondeja[107]	MC HB	6 mths	Participation SIS	NR	Gender mean 0.94 (95% CI -4.31, 6.18)		x		Age, stroke type, stroke severity, mRS, Fugl Meyer, Berg Balance Scale,

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Worse outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
										BI, walking velocity, therapy time
2008	Hommel[108]	SU SC HB Prosp	12 mths	Work and Social Adjustment Scale		Gender p=0.23		x		stroke severity, MMSE, PSD
2008	Lo[109]	HB Prosp	12 mths	LHS	NR	W:M OR 0.65 (95% CI 0.20, 1.09)		x		PSD, BMI, age, financial assistance, pain, proxy, death

*denotes studies designed to examine the sex differences in outcome
BMI: Body mass index; SC: single centre, MC: multi-centre, HB: hospital-based, PB: population-based, prosp: prospective study, retro: retrospective study, mths: months, yrs: years, RNLI: Reintegration to Normal Living Scale, SIS: Stroke Impact Scale, LHS: London Handicap Scale, FIM: Functional Independence Measure, MMSE: Mini Mental State Examination, PSD: post-stroke depression, mRS: modified Rankin Scale, NR: not reported

1.6.4 Health-related quality of life

Existing reviews of studies of HRQoL after stroke reported worse HRQoL after stroke in women compared to men in unadjusted analyses.[23,24] Despite the increased interest in sex differences, existing research has not adequately investigated the reasons for worse HRQoL in women, either in short or long-term studies. Age, sociodemographic factors, stroke severity, functional outcome and depressive symptoms were the most common contributing factors of the sex difference in HRQoL. Few studies examined whether differences in management after stroke influenced the sex difference in HRQoL. Some authors reported that difference in HRQoL between women and men still exists even after adjusting for some potential confounding factors.[24,98,110-115] while others show contrary findings or no significant difference between men and women in post-stroke HRQoL.[24,116]

The inconsistent findings on the sex difference may due to study design (e.g. only 2 out of 13 short-term studies were population-based; **Table 1-5**) to examine underlying reasons for the association between sex and HRQoL. Uncertainty exists over the causes of sex difference in HRQoL given variations in the outcome measurements, adjustment for different covariates, and methods of analysis.[23] As can be shown in **Table 1-5**, HRQoL up to 1 year after stroke has been assessed by several generic (i.e. European Quality of Life – 5 dimensions, 36-item Short Form Health Survey, 12-item Short Form Health Survey) and stroke-specific instruments (i.e. Stroke-Specific Quality Of Life; Stroke Impact Scale) while the unadjusted and adjusted results were reported in different scales such as mean difference or odds ratio. This calls for a

more comprehensive investigation of contributing factors to the sex differences in HRQoL following stroke.

Table 1-5. Summary of sex differences in health-related quality of life up to 1 year after stroke from studies with multivariable adjustment (source: Gall et al., 2018)[23]

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Good outcome in adjusted results			Adjustments
							Women < Men	Women = Men	Women > Men	
2016	Chang[117]	MC HB Prosp	6 mths	EQ5D			x			Age, severity, sociodemographic factors, functional outcome, aphasia screening
2016	Chuluunbaatar[118]	MC HB Prosp	1 yr	WHO QOL-BREF		W:M mean difference 6.5 (P<0.01)			x	Age, sociodemographic factors, functional outcome
2015	Guajardo[119]	SC HB Prosp	3 mths	SF36	M:F mean difference 0.048 (P<0.05)	M:F mean difference (95% CI) 7.61 (-1.88, 17.11; ns)		x		Age, sociodemographic factors, depression
2015	Lopez-Espuela[113]	SU SC HB Prosp	6 mths	SF12		W:M mean difference **MHSS**		x		Age, severity, sociodemographic factors, functional

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Good outcome in adjusted results			Adjustments
							Women < Men	**Women = Men**	**Women > Men**	
						0.162, (P=0.062) **PHSS** 0.204 (P=0.009)				outcome, comorbidities
2015	Reeves[120]	PB	3 mths	SSQOL		W:M mean difference (95% CI) -0.05 (-0.29, 0.19)		x		Age, sociodemographic factors, comorbidities, severity, tPA, functional outcome
2014	Bushnell[110]*	MC HB Prosp	3 mths, 1 yr	EQ5D	W:M mean difference (95% CI) **3 mths** -0.045 (-0.065, -0.025) **1 yr** -0.040 (-0.065, -0.150)	W:M mean difference (95% CI) **3 mths** -0.036 (-0.056, -0.016) **1 yr** -0.022 (-0.045, 0.00)	x			Age, sociodemographic factors, comorbidities, severity, medications, 3 mth functional outcome, place of residence

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Good outcome in adjusted results			Adjustments
							Women < Men	Women = Men	Women > Men	
2012	Abubakar[121]	SC HB Prosp	3 mths	SIS-16	M:W mean (SD) 56.6 (8.9) for men, 52.4 (10.5) (P=0.093)	M:W OR (95% CI; better HRQOL) 2.25 (0.45-11.23)		x		Age, sociodemographic factors, BP, functional outcome, depression
2011	Delcourt[122]	MC HB Prosp	1 yr	QOL35	good HRQoL: 70% M; worse QoL 57% M	M:W OR worse HRQOL 0.73 (95% CI 0.54, 0.98)	x			Age, stroke severity, sociodemographic factors, comorbidities, functional outcome
2010	Almborg[123]	SC HB Prosp	2-3 wks	SF36		W:M mean difference 0.073 (p=0.100)		x		Age, sociodemographic factors, treatment, functional outcome, PSD
2009	Shyu[124]	SC HB Prosp	1, 3, 6 and 12 mths	SF36		M:W mean difference **MHSS**:	x		x	Age, time of follow-up, sociodemographic factors, functional outcome

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Good outcome in adjusted results: Women < Men	Women = Men	Women > Men	Adjustments
						-3.634 (p=0.021) **PHSS**: 3.44 (p=0.018)				
2007	Gargano[104]*	MC HB Prosp	3 mths	SSQOL		W:M mean (SE) 4.0 (0.08) vs 3.5 (0.07; (p<0.001)	x			Age, sociodemographic factors, stroke type, pre-stroke ambulatory status, proxy, functional outcome
2007	Lindgren[125]	MC HB Prosp	3-12 mths	EQ5D		W:M mean difference (95% CI) -0.125 (-0.204; -0.045)	x			Age, severity, stroke type, stroke Hx, time of stroke
2007	Patel[49]	PB	1 yr	SF36	W:M mean (SD) **MHSS:**	W:M mean difference (95% CI)	x			Age, stroke, severity, sociodemographic

Year	Author	Design	Time	Measure	Unadjusted results	Adjusted results	Good outcome in adjusted results: Women < Men	Good outcome in adjusted results: Women = Men	Good outcome in adjusted results: Women > Men	Adjustments
					46.1 (12.4) vs 47.2 (11.8; p=0.464); **PHSS:** 38.3 (12.4) vs 35.6 (12.2; p=0.025)	**MHSS**: NS **PHSS**: -3.26 (-5.70, -0.81; p=0.009);				factors, comorbidities

*denotes studies designed to examine the sex differences in outcome
EQ5D: European Quality of Life – 5 dimensions; BP: blood pressure; SC: single centre, MC: multi-centre, HB: hospital-based, PB: population-based, prosp: prospective study, retro: retrospective study, DC: discharge, mths: months, Hx: history, BP: blood pressure, tPA: Tissue plasminogen activator, mths: months, yr: year, SF36: Short Form 36, SSQOL: Stroke-Specific Quality of Life Scale, WHOQOL-BREF: The Brief World Health Organization Quality of Life Assessment Instrument, SIS-16: Stroke Impact Scale-16, SE: standard error; QOL-35: 35-item quality-of-life questionnaire, yr: year; MHSS: mental health; PHSS: physical health; M: men; W: women; OR: odds ratio

1.7 Potential factors associated with sex differences in outcomes after stroke

1.7.1 Socio-demographics

One of the major reasons why women may have worse outcomes than men after stroke is that they are more likely to be older than men[55,83] by up to 5 years.[61,94,126-128] For example, women had a mean age of 72.9 years at stroke onset while among men the average age at first-ever stroke was 68.6 years.[129] Other evidence reveals that socioeconomic position may be important as it is associated with stroke risk profile[130] and severity of stroke[131] and is, therefore, an important contributor to poor outcomes after stroke.[130-133] Several studies reported lower socioeconomic position among women compared to men[134,135] including socioeconomic position,[134] educational level,[135] occupation,[135,136] and income.[132] This may, therefore, partly explain the sex differences in long-term outcomes of stroke. Given their advanced age at the time of stroke onset, women tend to more often be living alone[137] before stroke, even 3-6 months following stroke.[67] They are thus more likely to reside in an institution or have less social support after stroke[81,138] which are associated with poorer outcomes.[139,140] The effects of loneliness, social isolation, social support, and living alone on health outcomes have received increasing attention recently. Living alone is particularly important in older women because they are more than twice as likely to live alone than men (46% of women 75 years of age and older live alone compared to only 23% of men).[141]

1.7.2 Pre-stroke function, comorbidity, risk factors, stroke type and stroke severity

Women may have poorer physical function prior to stroke onset,[94,140,142,143] and more post-stroke depression than men.[143] In addition, sex differences in stroke risk factor profiles[99,144-148] and pathology[149] may partly explain why women often experience more severe stroke.[127,129] Women tend to more often have pre-existing hypertension and atrial fibrillation while smoking, alcohol overuse, peripheral disease prior to stroke are more often found in men.[81,140] The differences in risk factor profile have been suggested to account for the differences of stroke lesion patterns in genders. Evidence also shows that women were more likely to suffer from haemorrhage[84,145] and cardio-embolic infarction[83,144,150] whilst men develop large and small vessel diseases more often.[151]

1.7.3 Treatment and management

Current reviews articles on stroke indicated that it is under debate whether there are sex-related differences in stroke management.[80,84,149] When it comes to the time of arrival to emergency department from onset, a majority of studies showed no difference between men and women.[152-155] However, others reported greater pre-hospital delay among women than in men with stroke.[84,156,157] Also, women with acute stroke have been reported to experience greater emergency department delays than men, which were not attributable to differences in presenting symptoms, time of arrival, age, or other confounders.[158]

Some investigators from the United States of America and Europe have reported that women receive evidence-based care less often compared to men.[80,84] Studies indicated that there were sex differences in receipt of diagnostic and treatment-related procedures such as brain imaging and echocardiograms after accounting for age and stroke severity.[142,159] Others found that women were less likely to receive thrombolytic therapy,[160-162] and the difference remained significant even after adjustment for age, comorbidities like heart diseases, smoking and pre-stroke ambulatory status (e.g. walking ability).[102] This disparity may be due to the delayed time to hospital presentation in women,[163] which can limit the ability to receive this treatment. Although the evidence shows no sex difference in access to rehabilitation hospitals,[12] women may experience more difficulties in stroke recovery.[80,101] Risk of death or recurrence after stroke is substantial and profoundly influenced by sex and comorbidities[164] which may influence the differences in outcomes between two sexes. Therefore, how treatment and management contribute to sex differences in stroke outcome should be explored carefully.

1.7.4 Post-stroke factors

There is a relationship between psychological issues such as depression and cognitive impairment and outcomes of stroke. For example, emerging data reveal that post-stroke depression was associated with mortality,[165] worse functional outcomes[166] as well as reduced HRQoL.[166,167] A systematic review showed that prevalence of post-stroke depression was higher in women than in men[168] which may influence the sex differences in long-term outcomes of stroke.

1.8 **Summary**

Women appear to experience worse outcomes after stroke than men but the causes of these differences have not been conclusively determined in either short- or long-term studies. Potential factors associated with poorer outcomes in women included older age, lower socioeconomic position, living alone more often, having more pre-stroke functional limitation, comorbidities, severe strokes, and the presence of depression after stroke more often than men. There is also some evidence that women receive evidence-based care less often than men after stroke but how this influences outcomes after stroke is unclear. There is a need for high-quality studies to explore the sex differences in outcomes following stroke and contributing factors to inform interventions to address these differences.

Chapter 2: Methods for studies using data from population based stroke incidence studies: the INternational STRoke oUtComes sTudy (INSTRUCT)

2.1 Preface

The first four studies in this thesis use individual participant data (IPD) from 13 population-based stroke incidence studies worldwide. I used these data to examine the differences between men and women in various outcomes of stroke. This study — the INSTRUCT (INternational STRoke oUtComes sTudy) was an IPD meta-analysis on over 16,900 first-ever stroke cases. This chapter describes the methods for this study including settings, participants, outcome variables, covariates and statistical analyses techniques. More specific details of the statistical methods for each outcome after stroke are described in subsequent chapters (Chapter 3: mortality; Chapter 4: functional outcome and participation restriction; Chapter 5: HRQoL; Chapter 6: severity of stroke).

2.2 Ethics

The INSTRUCT was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0014861). All of the participating studies had signed informed consent from participants and approval from their respective local ethics committees.

2.3 **Study population and design**

The INSTRUCT is a collaboration between 13 'gold standard' stroke incidence studies conducted around the world between 1987 and 2014 (**Table 2-1**). The included studies represented 59% of the 22 potentially eligible studies identified by systematic search (see below for details of the search strategy, search term, data collection and data management). Investigators for these studies provided de-identified datasets containing the relevant variables to undertake our analyses. I created a pooled dataset and undertook statistical analyses to examine sex differences in long-term outcomes after stroke.

Table 2-1. Details of included cohorts

Study	ID	Study year	Baseline (n)
Oxford, United Kingdom	A	2002-2013	1374
Joinville, Brazil*	B	2011-2013	980
Melbourne, Australia	C	1996-1999	1316
Arcadia, Greece†	D	1993-1995	555
Perth, Australia	E	2000-2001	183
Orebro, Sweden	F	1999-2000	377
Dijon, France	G	1987-2012	4621
Martinique, West Indies	H	1998-1999	580
Porto, Portugal	I	1998-2000	688
Auckland, New Zealand	K	2002-2003	1423
L'Aquila, Italia	L	1994-1998	4353
Matão, Brazil	M	2001-2002	81
Tartu, Estonia†	N	2002-2003	433
Total cases			16,964

* Additional data from the Joinville study have been provided in mid-2017 when all the results of the first study of long-term mortality (Chapter 3) were finalised and published. The follow-up data up to 5 years of 2,448 first-ever strokes between 2009 and 2014 at baseline were, therefore, included in the following analyses on the long-term functional outcome and participation restriction, health-related quality of life and stroke severity at the time of stroke.

† only have 1-year follow-up data

Search strategy, search term, data collection and management

Our study was a collaboration between investigators for 13 population-based incidence studies identified through a previous systematic review (2008),[57] and our research networks. To understand how representative these studies were of all possible studies, the investigator team undertook a systematic literature search in 2015 of the literature published after the aforementioned systematic review, as detailed below.

2.3.1 Search strategy

We identified potential studies using previous systematic reviews of these 'ideal' stroke incidence studies[31,169] supplemented with an updated search for new studies published since May 2008, the end date for the systematic review by Feigin et al.[57] The Feigin's review aimed to identify worldwide population-based studies that reported stroke incidence and early case fatality. We systematically searched population-based studies from academic databases (PubMed, Scopus, Embase and ScienceDirect) aiming to identify all 'ideal' incidence studies conducted between May 2008 and May 2014 with terms "stroke", "isch(a)emic stroke", "intracerebral", "intraparenchymal", "subarachnoid", "h(a)emorrhage", "population-based", "community-based", "community", "epidemiology", "epidemiological", "incidence", "attack rates", "survey", "surveillance", "mortality", "morbidity", "fatality", "case fatality", or "trends".

The inclusion criteria were any stroke incidence study which met criteria of 'gold

standard',[31,169] restricted to human studies only and published in the English language. These studies have standardised methods to ensure high quality data, including standard definitions for first-ever-in-a-lifetime stroke; a prospective design, population-based case ascertainment from multiple overlapping sources from inside and outside hospital systems; subtyping of a large proportion of events using imaging; a large and preferably stable population base; and surveillance over at least one year to control for seasonal variation in stroke occurrence. The exclusion criteria were any population-based study which was not an adequate design (e.g. age limitations, ischaemic stroke only).

We then established whether investigators of all eligible studies identified by reviews and updated search had published on outcomes at 1 or more years after stroke. We then approached those who had published these outcomes to participate. Where repeat incidence studies with assessments were conducted over time, we requested access to the follow-up data from the most recent incidence study.

Two reviewers (Hoang Phan and Seana Gall) performed an online database search separately to identify eligible studies based on title or abstract and, where necessary, review the full-text articles. References list of studies were also searched for additional eligible articles and unpublished data from contact with authors. Each reviewer also performed an assessment to determine which studies met our inclusion criteria and all these activities were undertaken with each reviewer blinded to the results. Disagreements were resolved via consensus.

Our search strategy identified 28 new 'ideal' studies in addition to 56 population-based studies identified by the previous systematic review (Figure 2-1). Of these, 22 'ideal' population-based stroke incidence studies had published on follow-up of participants at 1 year or more after stroke. In 2014, the chief investigator approached investigators of 17 eligible studies with long term follow-up to participate, with 13 agreeing (**Figure 2-1**). The 13 studies were conducted in Australasia, Europe, South America, and the Caribbean (**Figure 2-2**). The main reasons for exclusion of 9 studies (**Table 2-2**) occurred due to refusal to participate (4 studies) and late identification of the study (5 studies).

Table 2-2. Eligible 'ideal' population-based studies of stroke for which long-term IPD were not provided

Study	Year	Follow-up time	Baseline (n)	Outcome	Results
Ludwigshafen, Germany[170]	'06-'07	1 year	725	Mortality	No sex-specific findings
Warsaw, Poland[42,171]	'05	1 year	127	Mortality	1-year crude CFR 24.1% for men vs 41.5% for women
South London, UK[48]*	'95-'06	up to 10 years	3373	Mortality, functional outcome	No sex-specific findings
Erlangen, Germany[33]*	'98-'06	up to 3 years	1631	Mortality	No sex-specific findings
Malmo, Sweden[172]*	'89-'92	3 years	2290	Mortality	1-year crude CFR 45.9% for men vs 54.1% for women
Aeolian Islands, Italia[173]	'99-'00	1 year	62	Mortality	No sex-specific findings
Vibo Valentia, Italia[174]*	'96	1 year	321	Mortality	No sex-specific findings
Rural Tanzania, Africa[89]	'03-'06	3-6 years	130	Mortality, functional outcome	1-year crude CFR 46.5% for men vs 44.3% for women
Valley of Aosta, Italy[175]	'04-'08	1 year	1326	Mortality, functional outcome	No sex-specific findings
Total n			9,985		

CFR, case fatality rate

*declined to participate

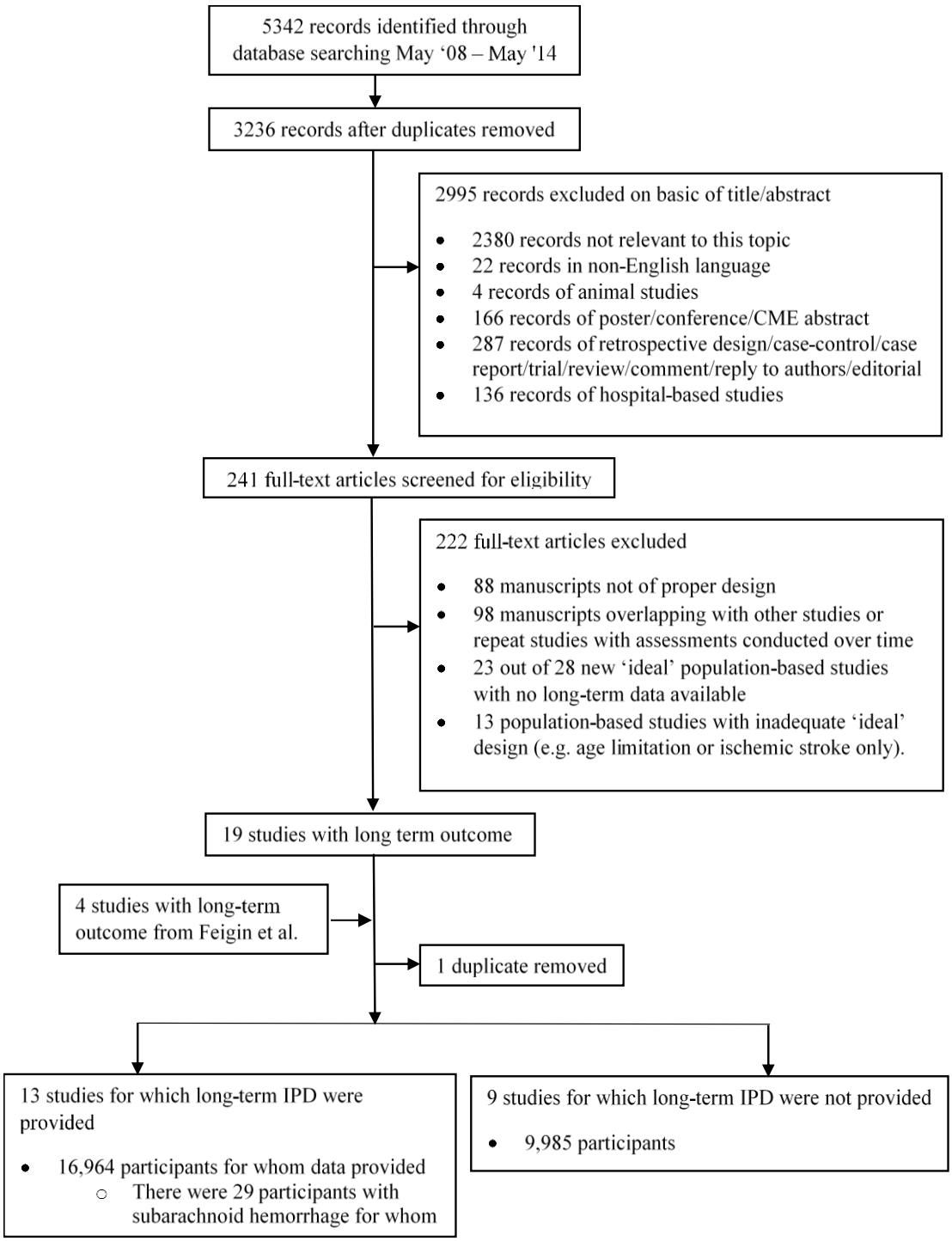


Figure 2-1. Flow diagram of potential stroke incidence studies

Of note, the studies without a proper design were those based on hospitals or other designs (e.g. randomised controlled trials, retrospective study, and case-control).

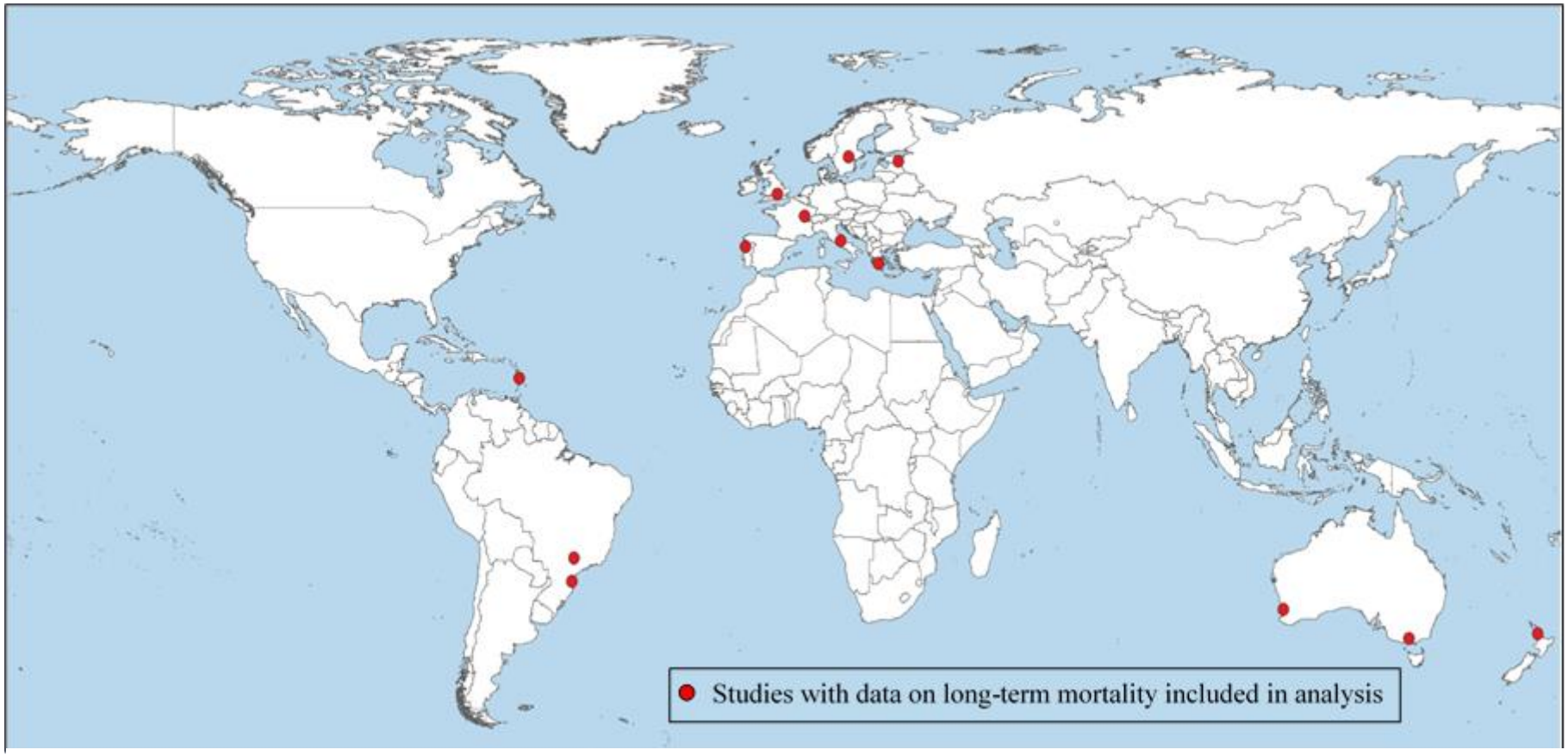


Figure 2-2. World map showing 13 population-based studies with data on long-term mortality of stroke included in the INternational STRoke OUtComes STudy

2.3.2 Search term

Pubmed (n=1851)

Search ((“stroke”[Title] OR “isch(a)emic stroke”[Title] OR “intracerebral”[Title] OR “intraparenchymal”[Title] OR “subarachnoid”[Title] OR “h(a)emorrhage”[Title])) AND (“population-based”[Title] OR “community-based”[Title] OR “community”[Title] OR “epidemiology”[Title] OR “epidemiological”[Title] OR “incidence”[Title] OR “attack rates”[Title] OR “survey”[Title] OR “surveillance”[Title] OR “mortality”[Title] OR “morbidity”[Title] OR “fatality”[Title] OR “case fatality”[Title] OR “trends”[Title]) Filters: Publication date from 2008/05/01 to 2014/05/01; English

Embase (n=721)

(1) 'population-based' OR 'community-based' OR 'community' OR 'epidemiology' OR 'epidemiological' OR 'incidence' OR 'attack rates' OR 'survey' OR 'surveillance' OR 'ideal study' OR 'mortality' OR 'morbidity' OR 'fatality' OR 'case fatality' OR 'trends' OR 'population-based' OR 'community-based' OR 'community' OR 'epidemiology' OR 'epidemiological' OR 'incidence' OR 'attack rates' OR 'survey' OR 'surveillance'

(2) 'stroke' OR 'ischaemic stroke' OR 'ischemic stroke' OR 'intracerebral' OR 'intraparenchymal' OR 'subarachnoid' OR 'haemorrhage' OR 'hemorrhage' AND .tw

(3) #1 AND #2 AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py), human, English

Scopus (n=1966)

Search (TITLE ("population-based" OR "community-based" OR "community" OR "epidemiology" OR "epidemiological" OR "incidence" OR "attack rates" OR "survey" OR "surveillance" OR "mortality" OR "morbidity" OR "fatality" OR "case fatality" OR "trends")) AND (TITLE ("stroke" OR "ischaemic stroke" OR "ischemic stroke" OR "intracerebral" OR "intraparenchymal" OR "subarachnoid" OR "haemorrhage" OR hemorrhage)) AND (LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011) OR LIMIT-TO (PUBYEAR, 2010) OR LIMIT-TO (PUBYEAR, 2009) OR LIMIT-TO (PUBYEAR, 2008)) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "ip")) AND (LIMIT-TO (LANGUAGE, "English"))

ScienceDirect (n=811)

Limitation: pub-date > 2007 and pub-date < 2015 and TITLE ("stroke" OR "ischaemic stroke" OR "ischemic stroke" OR "intracerebral" OR "intraparenchymal" OR "subarachnoid" OR "haemorrhage" OR “hemorrhage") AND TITLE ("mortality" OR "morbidity" OR "fatality" OR "case fatality" OR "trends" OR "population-based" OR "community-based" OR "community" OR "epidemiology" OR "epidemiological" OR "incidence" OR "attack rates" OR "survey" OR "surveillance")

2.3.3 Data collection

Authors of each eligible study (n=13 studies; **Table 2-1**) were contacted with a request for de-identified individual participant data (IPD) on stroke outcomes up to 5 years after stroke. Outcomes included mortality (date, time of stroke, date of death), functional outcomes and health-related quality of life. Data on participant characteristics were requested, if available, including (1) socio-demographics *(age, sex, marital status, education, occupation, socioeconomic position)*, (2) pre-stroke health including *body mass index, health behaviours (smoking, alcohol use), pre-stroke function (dependency, institutional residence), pre-stroke medication, history of comorbidities (atrial fibrillation, hypertension, ischaemic heart disease, peripheral vascular disease, transient ischaemic attack, diabetes, dementia)*, (3) stroke-related factors *(stroke severity, stroke type, year of stroke occurrence)*, (4) treatment and management *(hospital admission, time to hospital, admission and discharge medication, neuroimaging, carotid investigation, echocardiography and surgical intervention)* and (5) post-stroke factors *(depression and stroke recurrence)*.

Data provided were checked against published data, where possible, and if discrepancies were identified, clarification was sought from authors. When there was no response from authors, we checked whether results of sex differences were reported in published papers.

Available study factors for each study included in the INSTRUCT are provided in the **Table 2-3**.

Table 2-3. Study factors that are available in included cohorts

Study factors	Study ID*													Baseline n
	A	B	C	D	E	F	G	H	I	K	L	M	N	
Socio-demographics														
Age	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	16,645
Race/Ethnicity		✔	✔							✔			✔	3,450
Education	✔	✔	✔						✔	✔			✔	5,512
SEP	✔		✔		✔			✔	✔	✔				5,595
Marital status	✔					✔				✔			✔	3,255
Pre-stroke health														
Pre-stroke function	✔		✔		✔	✔	✔		✔			✔		14,799
Atrial fibrillation	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	16,645
Hypertension	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	16,645
IHD	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	16,645
PVD	✔		✔	✔		✔	✔	✔	✔		✔		✔	13,945
TIA	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	15,222
Diabetes	✔		✔	✔	✔	✔								3,836
Dementia				✔		✔			✔				✔	3,197
Smoking	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	16,212
Alcohol use	✔	✔	✔	✔	✔		✔	✔	✔	✔			✔	11,482
BMI	✔	✔			✔			✔	✔					4,329
Pre-stroke medication		✔	✔		✔					✔		✔		4016
Stroke-related factor														
Stroke severity	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	16,645
Stroke type	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		16,564
Treatment and management														
Time to admission	✔	✔			✔			✔	✔	✔		✔		5,284
Admission medication	✔	✔		✔	✔	✔			✔					7,336
Hospital admission	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	16,645
Investigations		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	15,271
Surgical intervention	✔	✔	✔				✔			✔				4,113
Discharge medication			✔		✔		✔	✔	✔				✔	8,443
Post-stroke factor														
1-yr depression			✔											1,316
5-yr depression			✔					✔		✔				3,319
1-yr stroke recurrence	✔		✔	✔			✔	✔	✔		✔		✔	13,568

5-yr stroke recurrence	✔	✔		✔	✔				7,999

* Study ID was described in Table 2-1
IHD=Ischaemic heart disease; PVD=peripheral vascular disease; TIA= Transient ischaemic attack; Body mass index=BMI; SEP=Socioeconomic position; yr:year

2.3.4 Data management

Study-specific outcomes and variable definitions (i.e. covariates) were recorded and, where necessary, recoded to create common variables with consistent definitions (e.g. stroke severity). Data collection methods of study factors across study are presented in Table 2.4. Following recoding, 13 datasets were then merged into one common database using study identification numbers.

2.4 Research questions

The research questions addressed in the part of thesis using the INSTRUCT data are highlighted below.

1) Are there differences between women and men in mortality up to 5 years after stroke? Which factors contribute to the sex differences?
2) Are there differences between women and men in functional outcome and participation restriction up to 5 years after stroke? Which factors contribute to the sex differences?
3) Are there differences between women and men in HRQoL up to 5 years after stroke? Which factors contribute to the sex differences?
4) Are there differences between women and men in severity of stroke at acute stage? Which factors contribute to the sex differences?

2.5 Measurement of potential confounding factors of sex difference in mortality in the long term after stroke

2.5.1 Socio-demographics

Data on age at the index stroke were available in all studies without age restriction. Race from studies from Joinville, Melbourne and Matão was categorised as Caucasian/Non-Caucasian. Educational level (6 studies: Oxford, Joinville, Melbourne, Porto, Auckland and Matão) was divided into two groups with the cut-off point of completing secondary education (grade 12). Classification of socioeconomic position (SEP) includes three groups: professional/non-manual (skilled + unskilled)/manual (skilled + unskilled) in 4 studies (Oxford, Melbourne, Perth and Auckland) whereas SEP was categorised as occupational/retired/unemployed & other in the Martinique and Porto studies. Data on marital status (5 studies: Oxford, Perth, Orebro, Auckland and Matão) were categorised into 2 groups: married/unmarried (single/divorced/widowed).

Table 2-4. Data collection methods of study factors across 13 studies

Study	Source of data
Oxford[176]	Pre-morbid medication and vascular risk factors were obtained from the patients or relative, hospital records, and general practice records. Blood pressure (BP) was recorded from the general practice records. Premorbid mRS was recorded from self-report questionnaire. Recurrent strokes were assessed during regular follow ups by a research nurse or therapist. If a recurrent vascular event was suspected the patient was assessed by a study doctor.
Joinville[177]	A self-reported history or current treatment for cardiovascular diseases and risk factors, smoking and alcohol was obtained from patients or their relatives by research nurses.
Melbourne[178]	Risk factors and management of risk factors were recorded by trained data collectors using a standardised questionnaire. Supporting data were collected from patients, relative, medical records and treating doctor. Dementia, hypertension, peripheral vascular disease (PVD), prior transient ischaemic attack (TIA), and prior myocardial infarction were defined as a known history. Diabetes was defined as either a known history or current presentation with fasting blood glucose ≥7.0 mmol/L. Atrial fibrillation (AF) was defined as either a known history or current presentation confirmed on ECG. Smoking status was classified from self-report as current smoker, ex-smoker, or never smoked. Prestroke disability was recorded from self-report questionnaire using Barthel Index. Recurrent stroke events were recorded by initial case finding methods or at annual follow-up interviews conducted by research nurses with possible recurrent event form. A panel of experts verified recurrent strokes using information from medical or nursing home records and from treating doctors.
Arcadia[179]	A history of hypertension was defined as systolic BP >160 mm Hg and/or diastolic BP >90 mm Hg ≥ 2 occasions before the stroke or documented treatment of hypertension. Diabetes was defined as use of a blood sugar lowering drug before stroke or a documented fasting blood glucose >120 mg/dl. AF was diagnosed by ECG for patients in hospital; for those not in hospital, at least one an ECG with documentation of AF in the year before the event was required. A history of TIA was defined when a patient had an attack diagnosed by a neurologist as a temporary, focal neurological deficit presumably related to ischaemia and lasting <24 hours. History of coronary heart disease (CHD) including myocardial infarction, angina pectoris and congestive heart failure was assessed by questionnaire without medical confirmation if it was diagnosed by a cardiologist and the patient had been given a relevant treatment.

Study	Source of data
	Smoking was considered present when a patient smoked daily prior to the stroke and was considered absent when the patient had never smoked or stopped smoking for ≥1 year before stroke. High alcohol consumption was defined as 60 g/day for men and 40 g/day for women.
	Premorbid mRS was recorded from self-report questionnaire.
	Recurrent stroke event was recorded during the follow-up.
Perth[180]	The presence of heart failure was based on clinical criteria that included one of the following: raised venous pressure, gallop cardiac rhythm (abnormal rhythm of the heart on auscultation), and crepitations at the base of the lungs. The presence of AF needed to be confirmed by an ECG within 1 month of the onset of stroke.
	Premorbid levels of physical disability were based on self-report or proxy sources (caregivers or medical records for those patients who were deceased or disabled) with the modified Barthel Index and mRS.
	Recurrence was recorded during the follow-up and confirmed by medical records.
Orebro[181]	A record of medical history was taken and logistic data regarding hospital treatment period, investigations were noted from medical records.
	Premorbid mRS was recorded from self-report questionnaire.
Dijon[52]	History of hypertension was defined as known hypertension in a patient's medical history (either self-reported or from medical notes) or if a patient was under anti-hypertensive treatment. History of AF, previous myocardial infarction, or TIA was recoded. Pre-stroke treatments by anticoagulants, antiplatelet agents and antihypertensive treatments were noted.
	Recurrent stroke was recorded during the follow-up and confirmed by medical records. It was classified as ischaemic or haemorrhagic, on the basis of a CT scan.
Martinique[182]	Hypertension was defined as known hypertension with antihypertensive therapy (the number of drugs was recorded) or systolic BP> 160 mm Hg and/or diastolic BP>90 mm Hg on ≥2 different occasions, the second one 1 week after stroke. AF was diagnosed when present on a standard 12-lead ECG. PVD was recorded on the basis of a history of intermittent claudication or previous arterial intervention or Doppler ultrasonography documentation. CHD was defined as history of acute myocardial infarction or angina pectoris.

Study	Source of data
	Smoking was defined as a cumulative consumption 10 pack-years. Alcohol abuse was diagnosed when the patient had a daily consumption 120 g. Recurrence was recorded during the follow-up. Survivors were interviewed by investigators with a questionnaire designed to detect recurrent cerebrovascular and cardiovascular events.
Porto[183]	Vascular risk factors were obtained from medical records from hospitals and/or general practitioners (GP). A history of hypertension was defined as systolic BP >160 mm Hg and/or diastolic BP >95 mm Hg ≥ 2 occasions before the stroke or documented treatment of hypertension. History of cardiac disease was defined as any previous diagnosis of angina, myocardial infarction or AF (confirmed by ECG). A history of TIA was recoded. Smoking was categorised as never smoked, former smoker for ≥1 year and current smoker. Pre-stroke disability was recorded from self-report questionnaire using Barthel Index. Recurrence was recorded during the follow-up. Medical records were used for follow-up purposes whenever the patient could not be contacted. The principal investigator reviewed the information collected for each patient. Throughout the study period, GPs received a report on their patients registered in the study, and every 2 months a periodic newsletter with the updated results was sent to all collaborators.
Auckland[184]	A self-reported history or current treatment for cardiovascular diseases and risk factors was obtained from patients or their relatives and then confirmed by medical records. History of hypertension was defined by self-report history of high BP or by the use of antihypertensive drugs. History of cardiac disease (AF, heart attack, angina, or other forms of heart disease). Smoking status (current smoker, former smoker for more than 1 year, never smoked) was defined by patients' self-report.
L'Aquila[36]	Hypertension was defined as known hypertension treated with antihypertensive therapy or systolic BP >160 mm Hg and/or diastolic BP >90 mm Hg on 2 different occasions. AF was confirmed by a standard 12-lead ECG. Coronary heart disease was defined as a history of acute myocardial infarction or angina pectoris. PVD was diagnosed in the presence of a history of intermittent claudication or previous arterial intervention or Doppler ultrasonography documentation.

Study	Source of data
	Smoking status was defined as never, current, and ex-smoker. Alcohol abuse was diagnosed in the presence of a daily consumption >120 g.
	Recurrent stroke was recorded during the follow-up with quarterly planned visits or with a structured telephone interview. It was defined as any new fatal and nonfatal event subsequent to the initial one, with an increased handicap at the time of the event, persisting beyond 24 hours.
Matão[40]	Risk factors and management of risk factors were recorded by trained data collectors using standardised questionnaire. Recurrence was recorded during the follow-up if there are any new episode of focal cerebral dysfunction persistence >24 hours.
Tartu[185]	Stroke risk factors were recorded based on case history and clinical evaluations. History of disease was obtained from outpatients and hospital records, family and patients. BP was measured at admission. AF was confirmed by ECG. Myocardial infarction was confirmed by ECG or autopsy.
	Premorbid mRS was recorded from self-report questionnaire.

2.5.2 Pre-stroke health

2.5.2.1 Co-morbidities

Co-morbidities included self-reported history of diabetes (4 studies: Oxford, Melbourne, Arcadia, Perth and Orebro), dementia (studies Melbourne, Orebro, Auckland and Matão), and cardiovascular diseases including ischaemic heart disease (all studies), atrial fibrillation (all studies), hypertension (all studies), transient ischaemic attack (all studies except the Auckland study), and peripheral vascular disease (studies Oxford, Melbourne, Arcadia, Orebro, Dijon, Martinique, Porto, L'Aquila and Matão) were performed (**Table 2-4**).

2.5.2.2 Body mass index

Body mass index was recorded in five studies: Oxford, Joinville, Perth, Martinique, and Porto.

2.5.2.3 Pre-stroke medication

Data on pre-stroke use of antihypertensive and antiplatelet agents were available in five studies (Joinville, Melbourne, Perth, Auckland, and Tartu) and information on use of anticoagulants before stroke was only available in the Melbourne and Auckland studies.

2.5.2.4 Health behaviours:

Smoking status, which was recorded in 12 studies (except the Tartu study), was categorised into 3 levels: never/former/current. Data on alcohol consumption were available in 11 studies. Alcohol use was classified as 3 groups – no/current drinkers/ex-drinkers (9 studies: Joinville, Arcadia, Perth, Dijon, Martinique, Porto, Auckland, Matão, and Tartu) or 4 groups – no/not heavy drinkers/heavy drinkers/ex-drinkers (3 studies: Oxford, Melbourne and Auckland).

2.5.2.5 Pre-stroke dependency

Pre-stroke functional status was assessed according to whether or not the patient was living independently before stroke in study Auckland, residing in an institution before stroke among 4 studies (Melbourne, Perth, Orebro and Dijon), the pre-stroke Barthel Index (BI) in 3 studies (Melbourne, Perth and Orebro) or pre-stroke modified Rankin Score (mRS) in 4 studies (Oxford, Perth, Porto and Tartu). Pre-stroke dependency or pre-stroke functional limitation was defined as pre-stroke BI<20 or pre-stroke mRS>2.

2.5.3 Stroke-related factors

2.5.3.1 Stroke type

Types of stroke, both ischaemic stroke and haemorrhagic stroke, were reported for all studies. We categorised stroke type into 4 groups: ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage (SAH) and undetermined stroke. Note that

these SAH cases were not followed up in Orebro (2.8%, 11/388 cases), Tartu (3.99%, 18/451 cases), and Melbourne studies (68/1316 cases).

2.5.3.2 Stroke severity

Items on loss of consciousness (6 studies: Melbourne, Arcadia, Dijon, Porto, Auckland, L'Aquila), paresis (6 studies: Melbourne, Arcadia, Dijon, Porto, Auckland, L'Aquila) and incontinence at onset (2 studies: Melbourne and Arcadia) were yes/no items used as markers of stroke severity. In the Dijon study, Barthel Index score (0-100) at admission, which was measured and categorised into 10 groups using a 10-point interval, were analysed as stroke severity. Barthel Index scores were reversed, with higher scores indicating greater severity of stroke, for analyses. Other assessments of stroke severity were the Glasgow Coma Scale (GCS)[186] with score ranging from 0 "coma" to 15 "alert" in studies from Arcadia, Auckland and Tartu and the Unified Neurological Stroke Scale (UNSS)[187] in the Porto study ranging from 0 to 33, with maximum score 33 for normal subjects. We analysed reversed scores for GCS and UNSS so that higher scores indicate more severe strokes for analyses. National Institutes of Health Stroke Scale (NIHSS)[188] was recorded in 7 studies (Oxford, Joinville, Melbourne, Perth, Orebro, and Dijon) with score ranging from 0-42, with larger scores indicating more severe stroke. Note that the NIHSS was measured in the Dijon study since 2008 only (n=1552). The Scandinavian Neurological Stroke Scale (SSS) was measured in the Matão study, with scores ranging from 0 (worst neurological deficit) to 58 (no neurological deficit). It was

mapped to the NIHSS (SSS = 50 – 2 x NIHSS)[189] for the purpose of comparing between studies.

2.5.3.3 Year of stroke occurrence

Data on the year the stroke occurred were available in all studies with ranges from 1987 to 2014. Additional data from the Joinville study were provided in the middle of 2017 after the first study of long-term mortality (Chapter 2), including first-ever strokes between 1987 and 2013, was published. The additional follow-up data up to 5 years of 2,448 first-ever strokes between 2009 and 2014 at baseline were included in the analyses on long-term functional outcome and participation restriction (Chapter 4), health-related quality of life (Chapter 5) and stroke severity at the time of stroke (Chapter 6).

2.5.4 Treatment and management

2.5.4.1 Hospital admission

All studies had data on whether or not people were admitted to hospital for their stroke.

2.5.4.2 Delay to hospital

Analyses of these data were based on the time from stroke onset to admission time in 7 studies. Out of these, studies from Martinique and Auckland only recorded time to hospital as ≤1 day/>1 day. Among the other 5 studies (Joinville, Melbourne, Arcadia, Porto and Tartu), we calculated the time to hospital from time of stroke onset to time

of admission and then categorised them into three groups (≤4.5 hours/4.5 hours-24 hours/>24 hours).

2.5.4.3 Admission medication

Three studies (Melbourne, Perth and Dijon) had data on treatment with antihypertensive agents at admission and four studies (Melbourne, Arcadia, Perth and Dijon) had data on antithrombotics, including antiplatelets and anticoagulants, at admission. Thrombolytic therapy (intravenous thrombolysis or rTPA) was also recorded in four studies (Joinville, Melbourne, Dijon and Auckland).

2.5.4.4 Investigation

Brain imaging (computed tomography— CT scan or magnetic resonance imaging —MRI) was recorded in all studies although we did not have the data for Oxford study. Carotid investigations during admission included carotid or transcranial Doppler (7 studies: Joinville, Melbourne, Arcadia, Dijon, Porto, L'Aquila and Tartu), CT or magnetic resonance angiography (3 studies: Melbourne, Martinique and Porto), and cerebral angiography (in 7 studies: Melbourne, Arcadia, Perth, Porto, Auckland, L'Aquila and Tartu). Cardiac investigations during admission included electrocardiography - ECG (9 studies: Joinville, Melbourne, Arcadia, Perth, Dijon, Porto, Auckland, L'Aquila and Tartu), echocardiography (7 studies: Melbourne, Arcadia, Perth, Dijon, Porto, Auckland and L'Aquila) and holter monitoring (3 studies: Melbourne, Porto and L'Aquila). In terms of surgical interventions, carotid

endarterectomy was recorded in studies from Oxford and Melbourne while coiling/clipping of SAH was recorded in studies from Oxford and Auckland.

2.5.5 Post-stroke factors

2.5.5.1 Depression

Depression was measured after 1 year and 5 years stroke in the study from Melbourne using the Irritability, Depression and Anxiety (IDA) Scale.[190] IDA was categorised with scores ≥ 8 defining depression.[191] In the Auckland study, depression at 5 years after stroke was recorded by sub-score of depression from the 28-item General Health Questionnaire (GHQ-28).[192] The Montgomery-Åsberg Depression Rating Scale (MADRS-S)[193] was recorded at 5 years after stroke in the study from Martinique, with the score ranging from 0 to 60. In the original study conducted in Martinique, investigators used a simplified MADRS version with a maximum score of 30, rather than 60, with scores ≥ 8 defining depression and scores ≥ 18 of 30, severe depression.[39]

2.5.5.2 Self-reported stroke recurrence

Stroke recurrence was recorded in most studies by participants reporting any stroke-like event since their last follow-up. In most studies, these events were verified against medical records, with a physician classifying the event as stroke or not. Data on recurrent stroke are available in 8 studies at 1 year follow-up (Oxford, Melbourne, Arcadia, Dijon, Martinique, Porto, L'Aquila and Matão) while 4 studies had data on

any recurrent stroke within 5 years after index event (Oxford, Melbourne, Dijon and Porto).

2.6 Study outcomes

2.6.1 Mortality outcome

All 13 studies gathered data on mortality at 1 year (n=16645) and 8 studies (n=12839) measured this at 5 years post-stroke (see **Table 2-5** for the source of mortality data). Nine studies also matched patients to national death registries (**Table 2-6**).

2.6.2 Functional outcome and participation restriction

Participants were followed up with face-to-face interviews conducted at 1 and 5 years after stroke in most studies. In two studies (Joinville and Tartu), mail or telephone interviews were used (**Table 2-6)**.

Functional outcomes or disability (**Tables 2-6 and 2-7**) were assessed by the modified Rankin scale (mRS) or Barthel Index (BI). Poor outcome was defined as mRS >2 (score 0-5) and BI<20 (score 0-20). Two studies (Melbourne and Auckland) had data on participation restriction assessed by the London Handicap Scale (LHS; score 0-100).

2.6.3 Health-related quality of life (HRQoL)

Analyses on HRQoL were based on assessments undertaken from 1 year and up to 5 year after stroke among stroke survivors (**Table 2-7**). Three instruments were used to

assess the HRQoL in the long term after stroke. In the Oxford study, HRQoL was assessed using the European Quality of Life–5 Dimensions (EQ-5D-3L) instrument.[194] For each of the five dimensions of the EQ-5D including mobility, self-care, usual activities, depression/anxiety, and pain), there are three response categories: no problem, some/moderate, and extreme problem. In the Melbourne study, the Assessment of Quality of Life (AQoL)[195] was used. The AQoL has five dimensions comprising illness, independent living, social relationships, physical senses, and psychological wellbeing with four response levels for each domain (from needing no help to requiring daily help). The Short Form–36 questions (SF36) was used to assess HRQoL among stroke survivors in the studies conducted in Perth and Auckland. The SF36 instrument covers both physical and mental health with eight sub-dimensions.

The EQ5D utility score was measured in the Oxford study but also mapped from modified Rankin Scale (mRS)[196] data among six studies with available data on the mRS at 1 and/or 5 years after stroke (**Table 2-7**).

Table 2-5. Source of mortality data across 13 population-based studies

Study	Source of data
Oxford[176]	Death data were obtained from medical records in hospital. Deaths out of hospital were identified via the Coroner's Office, by review of all death certificates in the study practices, and by ICD10 vascular death codes from the local Department of Public Health.
Joinville[197]	Death data were obtained from follow-up assessment and Death certificates
Melbourne[94]	Mortality was mostly recorded when contact was attempted for 1-year and 5-year assessments of functional outcomes. Matching of participants with the National Death Index provided mortality data for those lost to follow-up.
Arcadia[51]	Medical records for patients in hospital; general practitioners and private family physicians; health centres and death certificates.
Perth[46]	Vital status was initially ascertained by electronic linkage of Perth Community Stroke Study record to mortality data supplied by the Registrar General of Births, Marriages and Deaths for Western Australia.
Orebro[181]	Hospital discharge records and death certificates. Population statistics were used to ascertain whether a patient was still alive 1 year after stroke.
Dijon[52]	Death certificates obtained from the local Social Security Bureau that is responsible for registering all deaths in the community to identify fatal strokes occurring in non-hospitalised patients.
Martinique[39]	Survival status was ascertained from hospital records and death certificates
Porto[198]	Death data were obtained from follow-up assessment. Otherwise, a search was undertaken in the computer files held at the Northern Regional Health administration. In case of death, information about date and circumstances of death was confirmed by written monthly reports of death certificates at each health centre.
Auckland[53]	Hospital and other medical records, death certificates, and autopsy reports, and by maintaining regular contact with all long-term residential care facilities such as rest homes and private hospitals.
L'Aquila[36]	Death certificates were checked monthly, and clinical details of all deceased patients with a diagnosis of stroke, not otherwise included in the registry, were reviewed. The use of a case-finding method including multiple overlapping sources allowed an assessment of the completeness of case ascertainment by means of a capture-recapture technique.
Matão[40]	Death certificates were checked monthly, follow-up was assessed by hospital visits or telephone contact when moving to another city.
Tartu[199]	The survival was analysed using outcome data provided by the patients, by the National Population Registry and death certificates at Outpatient clinics.

Table 2-6. Source of functional outcome and participation restriction data across 11 population-based studies

Study	Source of data
Oxford[176]	All surviving cases were followed up by a research nurse or therapist at 12 months from the time of the stroke and modified Rankin Scale (mRS) score was calculated.
Joinville[197]	The functional outcomes were measured at 12 months and 5 years by telephone using the mRS.
Melbourne[94]	Survivors were interviewed in person; however, some telephone interviews were conducted. For those with cognitive or communication difficulties, a reliable proxy was sought. Interpreters were used when required. The functional outcomes were measured at 12 months and 5 years using Barthel Index, and the participation outcomes were measured at 5 years only using the London Handicap Scale. There was about 16% proxy response[200]
Arcadia[51]	For each patient with stroke, the mRS was applied at discharge from hospital and at the final follow up 1 year after stroke onset. Functional outcome for patients not in hospital was obtained by questionnaire from attending physicians or by examination of the patient at home.
Perth[46]	Patients not known to be deceased were sent a letter of invitation, which was followed by a telephone call or home visit. Those who agreed to participate were assessed at their usual place of residence by the study nurse. In addition to information regarding recurrent vascular events, major illnesses, and medications, this assessment included grading the current level of disability using the mRS.
Orebro[181]	Consultation visit and telephone interview. The functional outcomes were measured at 12 months (the mRS and Barthel Index).
Martinique[39]	Survivors were visited and underwent standardised interviews, conducted by visiting nurses, specially trained to apply different well-validated scales of evaluation. The functional outcomes were measured at 12 months and 5 years (the mRS).
Porto[198]	All patients were followed up by neurologists at 1 year and 7 years after the index event. Patients who collaborated but were not willing to complete the consultation were contacted by phone, and for those unable to come to the hospital, home visits were scheduled. Functional outcome was measured using the mRS.
Auckland[53]	After gaining verbal informed consent, subjects were interviewed via telephone to update details and complete a questionnaire. Participants were then invited to complete self-administered questionnaires. They were then contacted to arrange face-to-face interviews. Face-to-face interviews occurred at participants' usual places of residence and included neuropsychological tests and assessment of functional outcome at 1 year and 5 years (the mRS) and participation at 5 years (London Handicap Scale).

Matão[40]	All included cases were followed-up prospectively by the research team at 1 year after the stroke event with hospital visits. Patients unable to attend the scheduled visits or who had moved to another city were contacted by telephone. The functional outcome was measured at 12 months (Barthel Index).
Tartu[199]	The mRS assessments were made by the study physician by telephone at 1 year and 4 years after stroke. Barthel Index was evaluated at 1 year through questionnaire by post.

Table 2-7. Study outcomes in the included cohorts

	Severity	Mortality		Functional outcome		Participation restriction	Health-related quality of life	
Study	acute stage	1 year	5 year	1 year	5 year	5 year	1 year	5 year
Oxford	NIHSS	✔ *	✔ *	mRS	mRS		EQ5D/ mapped EQ5D	EQ5D/ mapped EQ5D
Joinville	NIHSS	✔		mRS	mRS		mapped EQ5D	mapped EQ5D
Melbourne	NIHSS	✔ *	✔ *	BI	BI	LHS	AQoL	AQoL
Arcadia		✔		mRS			mapped EQ5D	
Perth	NIHSS	✔ *		mRS			SF36 mapped EQ5D	
Orebro	NIHSS	✔ *	✔ *	mRS			mapped EQ5D	
Dijon	NIHSS	✔ *	✔ *					
Martinique		✔	✔	mRS	mRS		mapped EQ5D	mapped EQ5D
Porto		✔	✔	mRS	mRS		mapped EQ5D	mapped EQ5D
Auckland		✔	✔		mRS	LHS		SF36 mapped EQ5D
L'Aquila		✔	✔					
Matão	NIHSS	✔ *		BI				
Tartu	mapped NIHSS	✔ *		mRS	mRS		mapped EQ5D	mapped EQ5D

*denotes death data being matched to the national death registries

BI=Barthel Index; mRS=modified Rankin Scale; LHS=London Handicap Scale; NIHSS=National Institute of Health Stroke Scale; mapped EQ5D=EQ5D utility score was mapped from the mRS data; mapped NIHSS=NIHSS score was mapped from the Scandinavian Stroke Scale data.

Chapter 3: Sex differences in long-term mortality after stroke in the INternational STRoke oUtComes sTudy (INSTRUCT)

3.1 Preface

This thesis chapter has been published as a paper in the *Circulation: Cardiovascular Quality and Outcomes* (see **Appendix H**).

Phan H, Blizzard L, Thrift A, Cadilhac D, Sturm J, Heeley E, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Reeves M, Otahal P, Gall S. Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy). *Circ Cardiovasc Qual Outcomes*. 2017; 10. (Journal IF ~ 4.5; citation: 14). https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.116.003436.

This article was highlighted in the special edition 'Spotlight: Women and Heart Disease' of the Circulation: Cardiovascular Quality and Outcomes aligned with Go Red for Women® campaign by American Heart Association, which recognises that the burden of cardiovascular diseases in women is a major concern worldwide. This paper is accompanied by an editorial noting its novelty, significance and implications

for improving long-term outcome after stroke (see Editorial by Lisabeth and Madsen: https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.117.003546)

3.2 Abstract

Background: Women are reported to have greater mortality after stroke than men, but the reasons are uncertain. We examined sex differences in mortality at 1 and 5 years after stroke, and identified factors contributing to these differences.

Methods: Individual participant data for incident strokes were obtained from 13 population-based incidence studies conducted in Europe, Australasia, South America and the Caribbean between 1987 and 2013. Data on socio-demographics, stroke-related factors, pre-stroke health, and 1- and 5-year survival were obtained. Poisson modelling was used to estimate the mortality rate ratio (MRR) for women compared to men at 1 year (13 studies) and 5 years (8 studies) after stroke. Study-specific adjusted MRRs were pooled to create a summary estimate using random-effects meta-analysis. Overall, 16,957 participants with first-ever stroke followed up at 1 year, and 13,216 followed up to 5 years, were included. Crude pooled mortality was greater for women than men at 1 year (MRR 1.35, 95% CI [1.24-1.47]) and 5 years (MRR 1.24, 95% CI [1.12-1.38]). However, these pooled sex differences were reversed after adjustment for confounding factors (1 year MRR, 0.81, 95% CI [0.72-0.92]; 5-year MRR 0.76, 95% CI [0.65-0.89]). Confounding factors included age, pre-stroke functional limitations, stroke severity and history of atrial fibrillation (AF).

Conclusions: Greater mortality in women is mostly due to age but also stroke severity, AF and pre-stroke functional limitations. Lower survival after stroke among

the elderly is inevitable but there may be opportunities for intervention, including better access to evidence-based care for cardiovascular and general health.

3.3 Introduction

Women are reported to have greater mortality in the short term after stroke than men. In a review of 31 population-based studies of short-term mortality after stroke, Appelros and colleagues[129] reported that women had a 25% greater risk of 1-month crude mortality than men. It remains unclear what accounts for this disparity and whether these differences persist into the longer term. There have been no studies specifically designed to examine sex differences in long-term mortality after stroke.

Identifying factors that explain the sex differences in mortality is important because better understanding could lead to interventions to reduce the differences.[201] In an Australian study, the 36% greater risk of death at 28 days for women compared to men was explained by age, pre-stroke health, stroke severity and use of anticoagulants at discharge.[94] After adjustment in that study, women had a 17% lower short-term mortality than men. It is unknown whether these same factors account for the relative sex differences in other geographical regions or in long-term mortality.

Our aims were to quantify the relative sex difference in long-term mortality and to identify factors that contribute to the greater mortality of women after stroke using a meta-analysis of pooled individual participant data (IPD) from 13 ‘ideal’ incidence stroke studies conducted worldwide.

3.4 Methods

This study – the INternational STRoke oUtComes sTudy (INSTRUCT) – was registered in the international PROSPEective Register Of systematic reviews (PROSPERO; CRD42016036723)[202] and adhered to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD).[203]

INSTRUCT is an IPD meta-analysis of long-term outcomes after first-ever stroke. It included 13 'ideal'[31,169] population-based stroke incidence studies. These studies have greater internal validity and less selection bias than hospital-based studies.[28] The INSTRUCT study was a collaboration between investigators for 13 population-based incidence studies identified through a previous systematic review by Feigin et al.,[57] and our research networks. We requested de-identified IPD on mortality (up to 5 years after stroke) and participant characteristics from the investigators of 17 eligible studies with long term follow-up to participate, with 13 agreeing. To understand how representative these studies were of all possible studies, we undertook a systematic literature search in 2015 of the literature published since May 2008, the end date for the Feigin's review. The 13 included studies in the INSTRUCT represented 59% of the 22 potentially eligible studies later identified by our systematic search. The main reasons for exclusion of 9 studies occurred due to refusal to participate (4 studies) and late identification of the study (5 studies; see Methods **Chapter 2**: section **2.1**, **Figures 2-1** and **2-2**, and **Table 2-1** for full details of study selection).

3.4.1 Outcome measurement

The outcome was all-cause mortality at 1 year and 5 years after stroke. In 7 studies, mortality was obtained from national death registries (**Table 2-5**; **Chapter 2**). In the remaining 6 cohorts, a combination of hospital records, death certificates or direct participant follow-up was used. In four studies (Martinique, L'Aquila, Matão and Tartu) at 1 year and two studies at 5 years (Martinique and L'Aquila) vital status was recorded, but the exact date of death was not recorded (see 'Statistical analysis' for further details).

3.4.2 Study factors

The study factors assessed were those that might explain sex differences in mortality after stroke.[94] They included (1) socio-demographics, (2) pre-stroke health (dependence, co-morbidities and health behaviours), (3) stroke-related factors (stroke type, severity of stroke and year of stroke occurrence), (4) treatment and management, and (5) post-stroke factors (depression and recurrence). Details regarding how these data were collected and the definitions used for each variable in each specific study are provided in brief below and in full in the **Chapter 2** (**Table 2-5** and section **2.5**). In general, the patient or a proxy was interviewed within a few days of their event with clinical information supplemented from medical records and/or physician consultation, where possible.

Socio-demographic factors included age, sex, race/ethnicity, marital status, education, and socioeconomic status. Data on pre-stroke health status included dependence (retrospective modified Rankin scale, 4 studies; retrospective Barthel Index, 3 studies;

institutional residence, 4 studies and whether or not the patient was living independently before stroke, 1 study); co-morbidities (atrial fibrillation, hypertension, ischaemic heart disease, peripheral vascular disease, transient ischaemic attack, diabetes and dementia); medications before stroke (antihypertensives, antiplatelets, anticoagulants); body mass index; and health behaviours (smoking, alcohol use).

Stroke-related factors included the type of stroke categorised into 4 groups: ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage and undetermined stroke. Measurement of stroke severity included the National Institutes of Health Stroke Scale (NIHSS, 7 studies), Glasgow Coma Scale (3 studies), Unified Neurological Stroke Scale (1 study), Scandinavian Stroke Scale (1 study), Barthel index at onset (1 study) or loss of consciousness (6 studies), hemiparesis (6 studies) and incontinence at onset (2 studies).

Treatment and management included whether the patient was admitted to hospital; time delay to hospital presentation; thrombolytic therapy (rtPA); admission and discharge medications (antihypertensives, antiplatelets, anticoagulants); in-hospital investigations including neuroimaging (CT scan or MRI), carotid or transcranial Doppler, or echocardiography; and surgical interventions including carotid endarterectomy and aneurysm clipping or coiling.

Post-stroke depression was measured in 3 studies: the Irritability, Depression and Anxiety (IDA) Scale [190] was used in Melbourne (scores ≥ 8 defining depression),[191] the General Health Questionnaire (sub-score of depression)[192] in Auckland and the Montgomery-Åsberg Depression Rating Scale[193] (scores ≥ 8 defining depression)[39] in Martinique. Stroke recurrence was gathered by self-report of stroke-like events during

follow-up in 8 studies. In 6/8 studies (not including Arcadia and Matão), these events were verified by physician review of medical records.

3.4.3 Statistical analysis

Harmonising covariates across studies was not possible due to lack of uniform definitions. We, therefore, used the two-stage method of analysis proposed for IPD meta-analyses.[204] The first stage involved building study-specific crude and adjusted models to estimate the relative mortality rate ratio (MRR) for women compared to men. We used Poisson regression at 1 year (13 studies) and 5 years (8 studies) after stroke with the logarithm of the number of person-years at risk of dying within that period entered as an offset.[205] To undertake Poisson modelling in studies without exact date of death, multiple imputation by chained equations[206] (m=50 imputations) was used to impute person-years for men and women separately (see Supplement 3, 'Missing data and multiple imputation' for details). The role of covariates in the association between sex and mortality was determined using purposeful model building[207] to identify the significant confounders of sex difference in mortality. The following rules were applied to determine the covariates in the study-specific multivariable models: 1) the covariate was missing in <20% of cases; 2) the covariate was associated with mortality ($p<0.1$); 3) the covariate was associated with sex ($p<0.1$); and 4) the inclusion of the covariate in a model with only sex changed the magnitude of the sex coefficient by ≥10%.[207] Age and stroke severity were forced into the final multivariable models because they are well-established predictors of mortality and are associated with sex.[208] Covariates were transformed, as necessary using fractional polynomials in multivariable modelling[209], to get the best model fit.

We report fully adjusted models but also examine the effect of individual covariates on the sex difference in mortality. Within each study, statistical interactions were assessed by a test of statistical significance of a sex × covariate product term.

The second stage of the analysis involved combining the crude and adjusted study-specific effect estimates using random-effects meta-analysis. Statistical heterogeneity was evaluated using Q-statistics and I^2 statistics. Potential sources of heterogeneity were assessed among variables of study-level characteristics (e.g. geographic region, income group and severity instrument; **Supplemental Methods**: section **3.7.2**). Between-study interactions between sex and these study-level characteristics were assessed by meta-regression.

To further examine the robustness of our findings we also tested interaction effects using the single pooled individual participant data dataset.[210] In this data, we assessed the interaction between sex and participant-level covariates (stroke type, age at stroke onset and the year of stroke occurrence) by again testing the statistical significance of the sex × covariate product terms using multivariate random-effects meta-analysis.[211]

To describe the sex differences in crude mortality, Kaplan Meier survival curves by sex, accounting for study-specific curves, were estimated among the pooled IPD of studies with exact date of death to 1 year (9 studies) and 5 years (5 studies) after stroke.

Sensitivity analyses were used to examine the effect of the multiple imputation to account for unknown date of death or missing data, early deaths after stroke (e.g. 6

months) and, in a subset of studies, clinical treatment on the results (**Supplemental Methods**: section **3.7.2**).

Analyses were conducted in Stata 12.1. A two-tailed P-value ≤0.05 was considered statistically significant.

3.5 **Results**

There were 16,957 participants (13 studies; **Chapter 2: Table 2-7**) with data on 1-year mortality and 13,216 with data on 5-year mortality (8 studies). **Table 3-1** shows the baseline characteristics of each study population, further stratified by sex as shown in **Appendix A**: **Supplemental Tables A-1a** to **A-1c**. Women were older (statistically significant differences found in 10/13 studies) and more often unmarried (statistically significant difference 4/5 studies), living in institutions (statistically significant difference 3/4 studies) and functionally dependent before stroke (statistically significant difference 5/8 studies) than men (**Supplemental Tables A-1a** to **A-1c**). Women were more likely to be prescribed anti-hypertensive agents (statistically significant difference 3/5 studies) before stroke. In about half of the studies, women more often had an undetermined stroke type (statistically significant difference 6/12 studies) and had suffered more severe stroke than men (statistically significant difference 6/13 studies). In all studies, men were more often smokers (12/12 studies) or drinkers (10/10 studies) and more often had peripheral vascular disease (statistically significant difference 7/9 studies).

The crude survival rate using pooled IPD was 79.6% (men) and 68.5% (women) at 1 year (9 studies), and 58.7% (men) and 51.5% (women) at 5 years (6 studies; Figure

1). Data were available from 13 studies on 1-year mortality after stroke. The sample for complete-case analysis was n=14,972 cases (88% of available cases) due to missing data on some confounding factors. Women were 35% more likely than men to be deceased at 1 year in crude analyses (top panel, **Figure 3-2**) without evidence of heterogeneity (I^2=26.5, Q=16.3, p=0.177).

The direction of the pooled MRR was reversed in fully adjusted analyses, with women having lower 1-year mortality than men (adjusted MRR=0.81 [95% CI 0.72, 0.92]), albeit with some evidence of statistical heterogeneity (I^2=36.4, Q=18.9, p=0.092; bottom panel, **Figure 3-2**). The following covariates met our conditions for inclusion in the study-specific multivariable models (**Table 3-2**): age, stroke severity, stroke type, AF, pre-stroke dependency, smoking and history of peripheral vascular disease. There was limited evidence that other factors including socioeconomic status, cardiovascular risk factors and other comorbidities were responsible for the greater 1-year mortality in women (**Supplemental Table A-2**). Partial adjustment by inclusion of individual covariates changed the coefficient for sex difference substantially with age alone reducing the effect by 77%. Adjustment separately for stroke severity, AF, and pre-stroke dependency reduced the MRR by 42%, 5% and 45%, respectively (**Supplemental Table A-3**). There was no evidence that any of these covariates modified the effect of sex on mortality. In study-level analyses using meta-regression, difference in 1-year mortality (**Table 3-3**, 'study-level characteristics').

The sex difference in the adjusted MRR was less among studies with actual person-years than in studies with estimated person-years (adjusted MRR=0.74 vs 0.97, P=0.023, heterogeneity explained R^2=99.9%). Data were available from 8 studies on

5-year mortality after stroke. The sample for complete-case analysis was n=11,368 (86% of available cases). In crude analyses of 5-year mortality, women were 24% more likely than men to have died after stroke (top panel, **Figure 3-3**), but heterogeneity was significant (I^2=57.2, Q=16.4, p=0.022).

The direction of the 5-year pooled MRR (bottom panel, **Figure 3-3**) was again reversed on adjustment for covariates (adjusted MRR=0.76 [95% CI 0.65, 0.89]). However, there was significant heterogeneity in the study-specific multivariable estimates (I^2=69.1, Q=22.7, p=0.002). The factors most commonly adjusted for in the study-specific analyses were age, stroke severity, stroke type and AF (**Table 3-2**). There was limited evidence that other factors including socioeconomic status, cardiovascular risk factors and other comorbidities were responsible for the greater 5-year mortality in women (**Supplemental Table A-4**). Partial adjustment by inclusion of individual covariates changed the coefficient for sex difference substantially, age alone reversed the relative sex difference in 5-year mortality (pooled age-adjusted MRR 0.96 [95% CI 0.86, 1.08]; I^2=59.7, p=0.015). The effect was also reduced with separate adjustment for stroke severity (51%), AF (11%) and pre-stroke dependency (55%; **Supplemental Table A-5**). There was no evidence that any of these covariates modified the effect of sex on mortality. Meta-regression did not identify any sources of the heterogeneity observed in 5-year crude or adjusted models (**Table 3-4**, 'study-level characteristics').

In participant-level analyses of the single pooled IPD dataset using multivariate random-effects meta-analysis, estimations of the sex difference in unadjusted and adjusted mortality at either 1 or 5 years after stroke were independent of stroke type

and the year that the stroke occurred (**Tables 3-3** and **3-4**, 'participant-level characteristics'). As illustrated in **Figure 3-4**, the magnitude of the sex differences in mortality at 1 year or 5 years after stroke was not modified by age group.

Sensitivity analysis to account for missing data in one study with ≥ 20% missing data (Melbourne) using multiple imputation showed no difference in the estimated pooled effects for 1-year and 5-year mortality analyses when compared to complete-case analyses (**Supplemental Tables A-7a and A-7b**).

There was some evidence that the relative sex differences in 1-year and 5-year mortality were greatest in the first 6 months after stroke. The unadjusted female:male MRRs were reduced markedly by excluding deaths prior to 6 months with pooled MRR changing from 1.35 (95% CI 1.24, 1.47) to 1.14 (95% CI 0.92, 1.40) at 1 year and from 1.24 (95% CI 1.12, 1.38) to 1.07 (95% CI 0.92, 1.25) at 5 years (**Supplemental Table A-8**).

There was a variety of measures of treatment and management of stroke and its risk factors across studies. Significant differences existed in the prevalence of some of these between men and women but results were inconsistent across studies (**Supplemental Table A-9**). For example, women received less carotid investigations than men in 4/9 studies and underwent fewer echocardiography procedures in 3/7 studies but there were no sex differences in neuroimaging, thrombolysis, discharge medication and surgical intervention. However, there was very little evidence that these differences influenced the pooled female:male MRR at 1 or 5 years. With the exception of carotid investigations in Joinville, none of these factors confounded the Association between sex and mortality among hospitalised patients (**Supplemental**

A-10). In Joinville, adjustment for carotid investigations reduced the 1-year MRR by 59% among hospitalised cases. Nevertheless, the pooled estimates of the MRR for women compared to men were virtually unchanged by the revised estimate for Joinville (**Supplemental Table A-11**).

3.6 **Discussion**

We found that the crude sex differences in long-term mortality after stroke were consistent across time periods and various regions of the world. Compared to men, women were 35% more likely to die by 1 year and 24% more likely to die by 5 years after stroke, consistent with the 25% greater case fatality for women at 1 month reported in a previous review.[129] Our meta-analysis of this large individual participant dataset demonstrated that the greater mortality after stroke in women was mostly attributable to their advanced age but that greater stroke severity, greater pre-stroke functional limitations and the presence of AF also explained the difference. The substantial sex difference in crude mortality rates was reversed after accounting for these confounding factors. This finding suggests that the sex difference in mortality is largely due to biological and clinical differences between men and women present before or at the time of stroke while there was little evidence that differences in clinical management influenced the sex difference in mortality.

Age was the most important contributor to the sex difference in long-term mortality after stroke but there was no statistical evidence of effect modification by age. This is potentially due to reduced functional capacity of brain cells to recover after neurological insults,[212] but it may also reflect other age-related factors such as co-morbid disease, functional limitations or social isolation.[213] Older age may also

contribute to the worse stroke outcomes through reduced access to evidence-based stroke care,[214] particularly under-investigation and under-treatment of carotid disease in the elderly with stroke.[215] Limited treatment of elderly people, who are predominantly women, may be appropriate given their health profile, potential contraindications to some treatments,[216] and preferences for end-of-life care. However, it is also possible that by building the evidence base for stroke prevention and clinical management in the elderly,[217] and ensuring access to currently available evidence-based care for them, we could improve outcomes for men and women after stroke.

Women's greater mortality after stroke was attributable to their pre-stroke function, which is also closely related to their advanced age. There are sex differences in the specific causes of healthy life lost by age.[218] In men they are mostly respiratory and cardiovascular conditions, whereas in women, they are most often musculoskeletal and mental disorders. It is possible that better chronic disease management targeting these conditions could improve function[219] and prevent frailty[220] thereby improving the capacity to recover from stroke if it were to occur. Although we did not find evidence that social or economic factors influenced the sex differences in mortality, others have highlighted the influence of these factors across the life course on women's health.[221]

Atrial fibrillation also contributed to the sex difference in long-term mortality after stroke. Women with AF have a greater risk of stroke than men and AF-related stroke is more severe.[222] Management of AF in respect of proportions treated with anti-coagulants[223] or catheter ablation[224] appears suboptimal for women compared to men.

This observation is mostly biased by age with the widespread under-treatment of older patients with AF.[225] This highlights the need of better detection and treatment of AF in both elderly men and women prior to stroke.

We found that stroke severity was an important confounder. Although there were statistically significant sex differences in stroke severity in 6/13 studies, the magnitude of differences between men and women were quite small. The differences in stroke severity between men and women are not well understood but may include sex differences in the localisation of brain function,[226] and women's greater susceptibility to subarachnoid haemorrhagic or cardioembolic strokes than men.[226] Stroke severity could be modified through better management of risk factors associated with stroke severity such as hypertension, AF, diabetes,[227] and better acute stroke management.[228]

Our meta-analysis revealed that the sex differences in mortality were greatest in the first 6 months following stroke (Supplemental Table A-8) supporting previous research.[229] Evidence has shown that women with stroke suffer a disproportionately higher risk for death from cerebrovascular diseases while men are more likely to die from cardiac disorders and other diseases.[230] The causes of death differed by the time intervals from the stroke,[35] but little is known about differences by sex and age group. Examination of causes of death by sex and age group could identify ways to reduce disparities between men and women in mortality but such analyses were beyond the scope of our study. Further research is warranted to explore these differences after stroke and whether they are modifiable.

3.6.1 Limitations and strengths

A number of limitations need to be noted. Some potential confounding factors were not measured including hormonal, social and some demographic factors, particularly race or ethnicity (only available in Joinville, Melbourne and Matao). Missing data on confounding factors for some participants decreased the number of cases in fully adjusted analyses. Whilst we cannot discount the possibility of bias, sensitivity analyses which replaced missing data using multiple imputation did not markedly change the estimates suggesting that the missing data did not greatly influence our results. The studies were mostly from high-income countries (HICS), so the results might not be generalisable to low- and middle-income countries (LMICs). However, the magnitude of the sex differences and the contributing factors, were the same for the studies in LMICs as in HICs (**Tables 3-3** and **3-4)**. Among 9 'ideal' stroke cohorts for which long-term IPD were not provided, sex-specific findings from 3 studies showed similar differences in long-term crude mortality between women and men (**Chapter 2**: **Table 2-2**), suggesting the results would not be greatly different had they been included. There were also limited data on management of stroke, post-stroke recurrence and depression. However, among studies with comprehensive data on these 3 factors, the sex difference in mortality was not attributable to any of these factors. The single exception was the Joinville study, for which carotid investigation explained part of the sex difference. In summary, we think that the absence of this data is unlikely to have greatly affected our results. The 5-year pooled estimates may have lower statistical power because few studies had follow-up into the long term resulting in less than the recommended 10 studies for a meta-analysis.[231] There is also likely to be heterogeneity in the measurement of confounders across studies,

particularly vascular risk factors. This may have resulted in measurement error in some studies and affected the adjusted estimates.

Despite these limitations, our study has a number of strengths. This is the first IPD meta-analysis to explore the magnitude and causes of sex difference in both short- and long-term mortality after stroke. The data came from high-quality and generalisable studies free of the limitations of hospital-based or convenience samples. We had a very large number of participants, making this study adequately powered to test our hypotheses.

3.6.2 Conclusion

Our results indicate that women consistently have greater unadjusted long-term mortality after stroke than men. These differences were reversed after adjustment for confounders indicating that greater mortality in women is explained by their greater age, greater stroke severity, worse pre-stroke function and the presence of atrial fibrillation. The overwhelming importance of age in explaining the sex difference suggests that better stroke prevention and clinical management in the elderly is paramount to reduce the overall burden of stroke in men and women.

Table 3-1. Baseline characteristics of participants with first-ever stroke cases from 13 population-based stroke incidence studies

Study	Study year	Region	Baseline (N)	Women (%)	Ischaemic (%)	Age, median	1-yr mortality	5-yr mortality
Oxford, UK	2002-2013	Europe	1374	50.7	80.3	76.8	✓	✓ (n=760) §
Joinville, Brazil	2011-2013	South America	980	48.3	80.5	64.0	✓	
Melbourne, Australia	1996-1999	Australasia	1316	55.6	70.0	77.2	✓	✓
Arcadia, Greece	1993-1995	Europe	555	44.3	67.6	77.0	✓#	
Perth, Australia	2000-2001	Australasia	183	52.5	76.5	77.4	✓	
Orebro, Sweden	1999-2000	Europe	377†	55.2	72.7	78.0	✓	✓
Dijon, France	1987-2012	Europe	4621	53.1	82.7	77.7	✓	✓ (n=3719) §
Martinique, FWI*	1998-1999	Caribbean	580	50.9	76.6	73.0	✓	✓
Porto, Portugal	1998-2000	Europe	688	58.7	76.2	73.0	✓	✓
Auckland, NZ	2002-2003	Australasia	1423	53.1	72.5	74.0	✓	✓
L'Aquila, Italia	1994-1998	Europe	4353	52.9	82.6	75.9	✓	✓
Matão, Brazil	2003-2004	South America	81	37.0	84.0	65.0	✓	
Tartu, Estonia	2002-2003	Europe	433†	59.1	76.7	73.0	✓	
Total cases			16,964‡				16,957	13,216

✓ denotes studies with data

* FWI, French West Indies

† Baseline data without including cases of subarachnoid haemorrhage (Orebro 11 cases, Tartu 18 cases)

‡ Total cases including those with subarachnoid haemorrhage in all studies were 16,993

§ Follow-up data were available only among cases with year of stroke from'02-'08 for Oxford and '87-'08 for Dijon

There were seven cases who were lost-to-follow-up when comparing to baseline

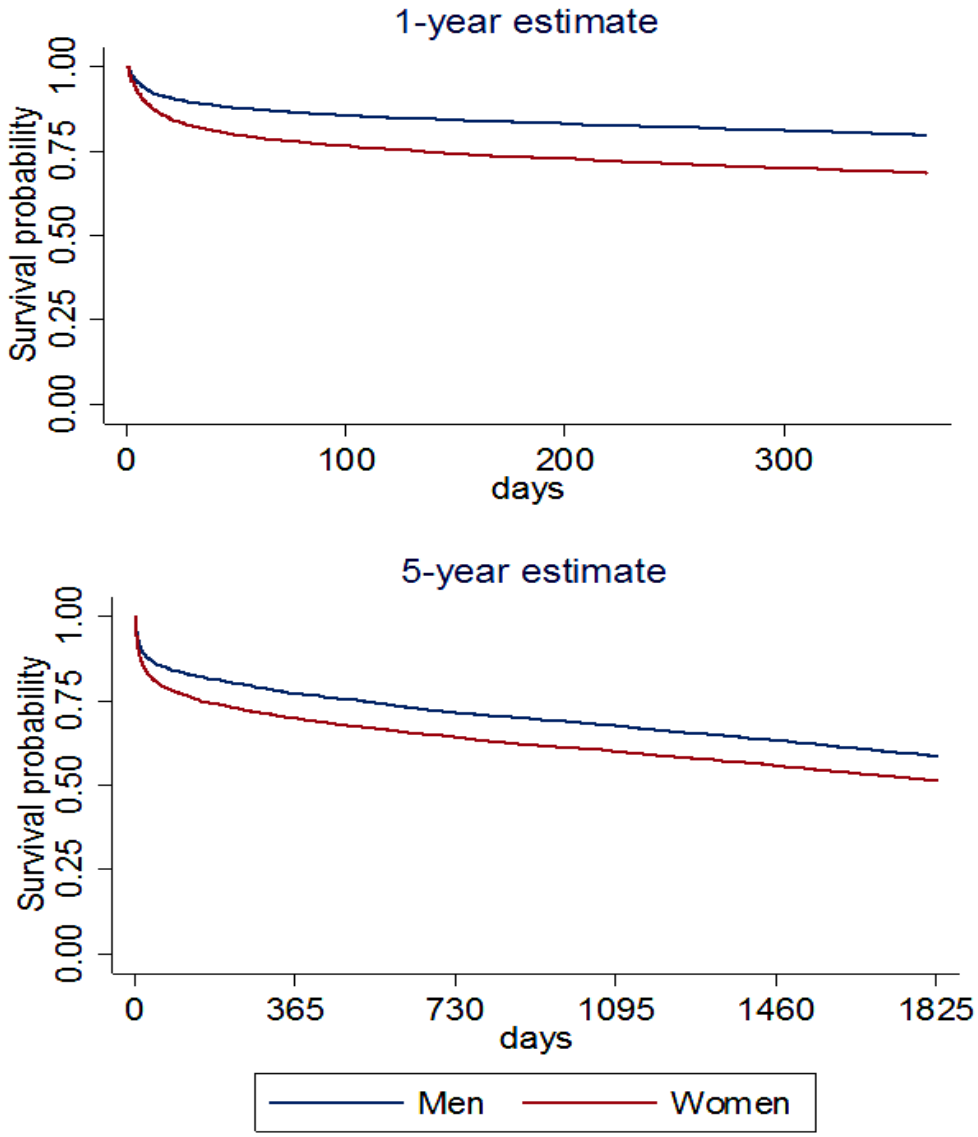


Figure 3-1. Kaplan Meier survival curves showing survival for men and women after stroke using pooled data among nine cohorts with 1-year follow-up (top panel) and among six cohorts with 5-year follow-up (bottom panel) accounting for study-specific curves

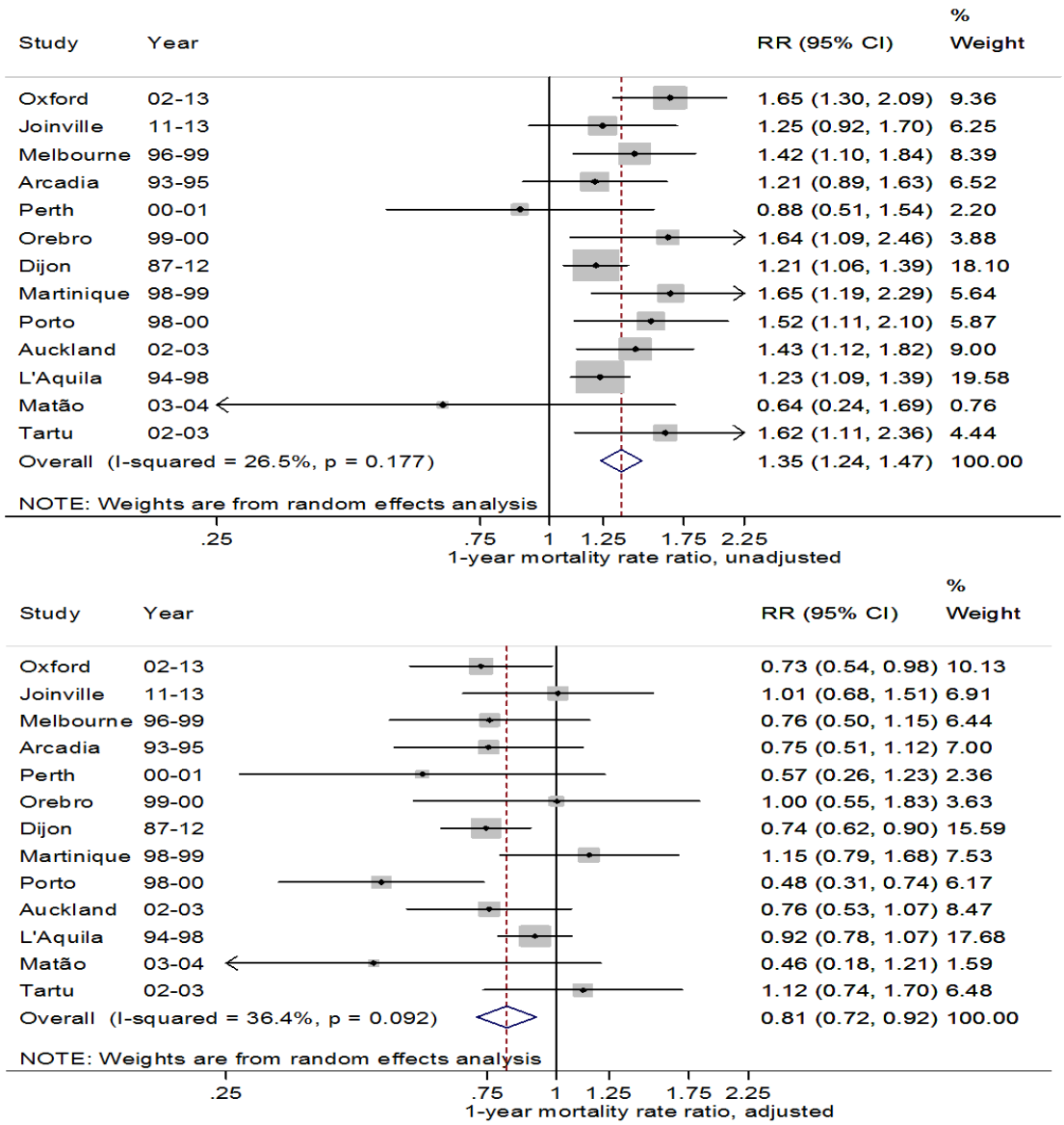


Figure 3-2. Mortality rate ratio (MRR) for women compared to men at 1 year after stroke in unadjusted (top panel) and adjusted (bottom panel) models from 13 studies combined using random effects meta-analysis (n=14,972).

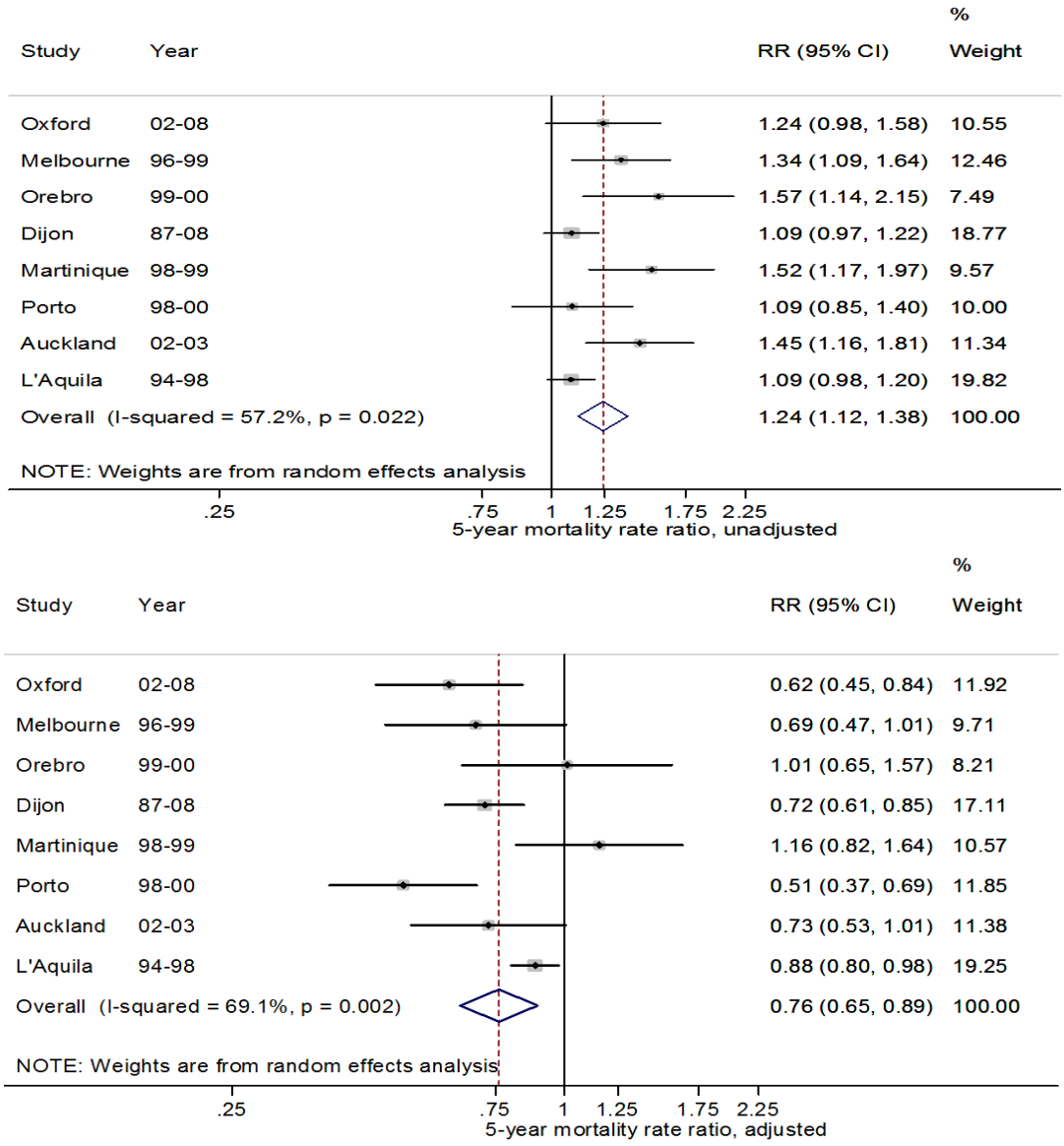


Figure 3-3. Mortality rate ratio (MRR) for women compared to men at 5 years after stroke in unadjusted (top panel) and adjusted (bottom panel) models from eight studies combined using random effects meta-analysis (n=11,368).

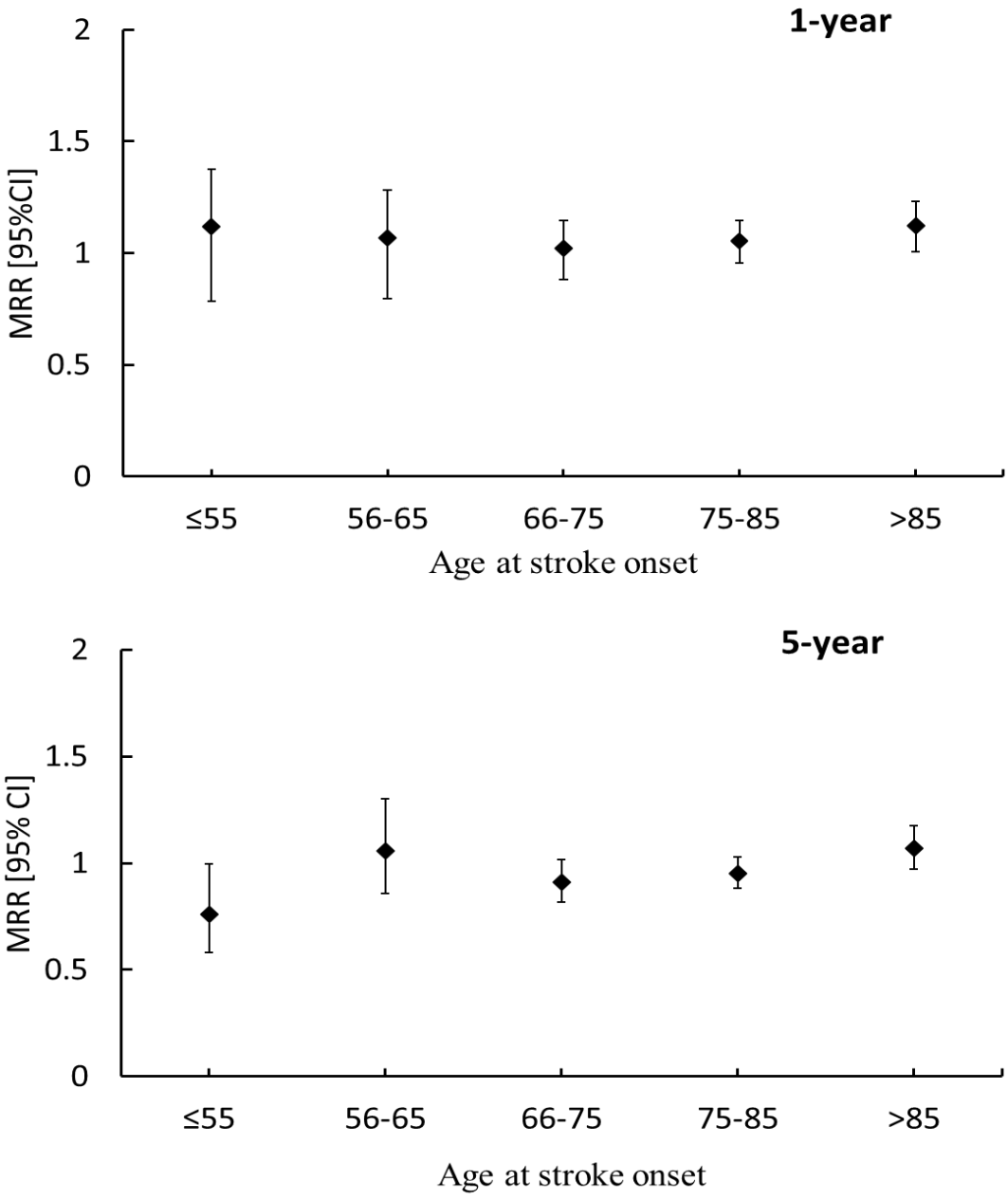


Figure 3-4. Unadjusted mortality rate ratio (MRR) with 95% Confidence Interval [CI] at 1 year (top panel) and 5 years (bottom panel) after stroke for women and men by age at stroke onset.

Table 3-2. Factors contributing to sex difference in long-term mortality between women and men after stroke based on the best fit sex-specific model within studies. Of note, covariates were transformed, as necessary to get the best model fit.

Study	1-year		5-year	
	N*	Actual confounding factors included in the fully adjusted model	N*	Actual confounding factors included in the fully adjusted model
Oxford	1290	age^3†, NIHSS (2-term)†, pre-stroke mRS, stroke type	732	age^3†, NIHSS (2-term)†, pre-stroke mRS
Joinville	979	age^3†, NIHSS, stroke type	-	
Melbourne	975	age, log NIHSS†, pre-stroke Barthel (2-term)†, AF, stroke type	975	age, log NIHSS†, pre-stroke Barthel (2-term)†, AF, stroke type
Arcadia	547	age, GCS, AF	-	
Perth	183	age, NIHSS, pre-stroke mRS, stroke type	-	
Orebro	377	age, log NIHSS†, institutional residence, stroke type	377	age^3†, log NIHSS†, institutional residence, stroke type
Dijon	3994	age^3†, LOC, AF, smoking	3094	age^3†, LOC, AF, smoking, stroke type
Martinique	569	age^3†, Barthel at onset (2-term)†, history of PVD	569	age^3†, Barthel at onset (2-term) †
Porto	650	age, LOC, smoking, pre-stroke mRS	650	age, LOC, pre-stroke mRS^2†
Auckland	1177	age^3†, log GCS†, pre-stroke dependence‡, AF, stroke type	1177	age^3†, log GCS†, pre-stroke dependence‡, AF
L'Aquila	3794	age, LOC§, AF, hospital admission, stroke type, smoking	3794	age, LOC§, AF, hospital admission, stroke type
Matão	79	age§, NIHSS	-	
Tartu	358	age, log NIHSS†	-	
Total cases	14972		11368	

AF, Atrial fibrillation; Barthel, Barthel Index; GCS, Glasgow Coma Scale; LOC, loss of consciousness (at onset); mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease.

* The sample size were the same among the unadjusted model and fully adjusted model; † Transformations were based on the powers (e.g. 3rd power, two power terms) suggested by fractional polynomials that produced the best-fitting multivariable model; ‡ Self-reported data regarding whether the patient lived independently before stroke; § Not meeting criteria of being a confounder but remain in the fully adjusted multivariable model

Table 3-3. Analyses of heterogeneity in sex difference in mortality at 1 year after stroke among 13 population-based studies

Variables of interest		No of studies	No of death (n/N)		Unadjusted				Adjusted*			
			Men	Women	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$
Study-level characteristics†												
Geographic region	Australasia	3	380/1339	584/1583	22.6	0.275	1.35 (1.10-1.65)	0.618	0.0	0.794	0.73 (0.57-0.94)	0.479
	Europe	7	1684/5830	2297/6564	36.2	0.152	1.35 (1.21-1.50)		50.7	0.058	0.80 (0.68-0.94)	
	South America	2	103/558	105/503	39.1	0.200	1.06 (0.60-1.86)		53.7	0.142	0.78 (0.38-1.59)	
	Caribbean	1	76/285	113/295	NA	1.000	1.65 (1.19-2.29)		NA	1.000	1.15 (0.79-1.68)	
Income group	HIC	10	2064/7169	2881/8147	26.4	0.201	1.34 (1.23-1.47)	0.948	32.0	0.152	0.79 (0.69-0.89)	0.186
	LMIC ‖	3	179/843	218/798	49.8	0.137	1.31 (0.92-1.86)		33.3	0.223	0.98 (0.69-1.39)	
Person-years	Actual	9	1394/5450	1940/6060	20.1	0.264	1.35 (1.22-1.49)	0.904	0.0	0.471	**0.74 (0.66-0.84)**	**0.023**
	Estimated	4	849/2562	1159/2885	50.8	0.107	1.37 (1.08-1.73)		24.2	0.266	0.97 (0.80-1.18)	
Death Registries	Yes	7	1042/3912	1482/4473	48.4	0.071	1.37 (1.16-1.62)	0.831	0.0	0.452	0.77 (0.68-0.88)	0.594
	No	6	1201/4100	1617/4472	0.0	0.466	1.31 (1.20-1.43)		56.5	0.043	0.83 (0.68-1.02)	
Age difference§	≤ 4.5 years	5	934/3002	1149/3143	0.0	0.556	1.21 (1.09-1.34)	0.057	5.8	0.374	0.87 (0.75-1.01)	0.673
	> 4.5 years	8	1309/5010	1950/5802	20.1	0.270	1.44 (1.30-1.59)		46.0	0.073	0.80 (0.67-0.95)	
Severity instrument	NIHSS	7	687/2561	959/2731	15.5	0.311	1.41 (1.24-1.61)	0.198	0.0	0.639	0.78 (0.66-0.93)	0.345
	Barthel	1	76/285	113/295	NA	1.000	1.65 (1.19-2.29)		NA	1.000	1.15 (0.79-1.68)	
	Others#	5	1480/5166	2027/5919	14.9	0.319	1.27 (1.15-1.39)		64.3	0.024	0.79 (0.64-0.97)	
SAH data	Yes	11	2132/7666	2898/8481	28.5	0.174	1.32 (1.32-1.45)	0.210	38.5	0.093	0.79 (0.69-0.90)	0.166
	No	2	111/346	201/464	0.0	0.971	1.63 (1.23-2.15)		0.0	0.766	1.08 (0.77-1.52)	
Sample size	≤ 250	2	49/138	39/126	0.0	0.574	0.82 (0.50-1.32)	0.134	0.0	0.745	0.53 (0.29-0.96)	0.321
	> 250−1000	6	451/1730	643/1876	0.0	0.589	1.44 (1.26-1.65)		58.3	0.035	0.88 (0.67-1.16)	
	> 1000	5	1743/6144	2417/6943	40.9	0.149	1.33 (1.20-1.48)		0.0	0.422	0.82 (0.74-0.90)	

Variables of interest		No of studies	No of death (n/N)		Unadjusted				Adjusted*			
			Men	Women	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$
Participant-level characteristics‡												
Stroke type	IS	13	1551/6419	2076/6993	39.0	0.073	1.33 (1.20-1.49)	Ref	35.5	0.098	1.01 (0.91-1.12)	Ref
	ICH	13	443/1001	552/1035	26.2	0.179	1.35 (1.09-1.66)	0.894	51.2	0.017	1.22 (0.96-1.55)	0.940
	SAH	10	87/241	137/358	8.3	0.365	1.11 (0.77-1.60)	0.318	78.0	<0.001	0.85 (0.40-1.80)	0.390
	Undetermined	12	172/351	364/559	0.0	0.633	1.53 (1.19-1.98)	0.370	80.9	<0.001	0.91 (0.56-1.47)	0.449
Age group	≤65	13	334/2295	243/1620	0.0	0.504	1.06 (0.89-1.27)	Ref	-			
	>65-75	13	537/2350	446/1935	0.0	0.489	1.08 (1.00-1.17)	0.337	-			
	>75	13	1372/3367	2410/5390	0.0	0.603	1.12 (0.99-1.28)	0.404	-			

Bold denotes statistically significant results; P^H, P-value of heterogeneity; $P^{sub-group}$, P-value for subgroup analysis; Ref, reference group; NA, not applicable; IS, Ischaemic stroke; ICH, Intracerebral haemorrhage; SAH, Subarachnoid haemorrhage; Barthel, Barthel index (at onset), NIHSS, National Institutes of Health Stroke Scale; MRR (95% CI), Mortality rate ratio (95% confidence interval) between women and men; HIC, High-income country; LMIC, Low- and middle-income country.

* MRR adjusted for actual confounders, but estimates for stroke type adjusted for age only; † Estimates were performed using two-stage method analysis; ‡ Estimates were performed using multivariate random-effect meta-analyses from a pooled dataset; § Indicates difference in median age at onset between women and men; || Low- and middle-income country (LMIC) group included studies conducted in Martinique, Joinville and Mãtao; # Other instruments including Glasgow coma scale and loss of consciousness

Table 3-4. Analyses of heterogeneity in sex difference in mortality at 5 years after stroke among 8 population-based studies

Variables of interest		No of studies	No of death (n/N)		Unadjusted				Adjusted*			
			Men	Women	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$
Study-level characteristics†												
Geographic region	Australasia	2	508/1252	758/1487	0.0	0.614	1.39 (1.19-1.61)	0.080	0.0	0.835	0.71 (0.56-0.91)	0.308
	Europe	5	2306/4596	2832/5301	29.8	0.223	1.13 (1.04-1.24)		77.1	0.002	0.73 (0.59-0.89)	
	Caribbean	1	135/285	180/295	NA	1.000	1.52 (1.17-1.97)		NA	1.000	1.16 (0.82-1.64)	
Income group	HIC	7	2814/5848	3590/6788	51.7	0.053	1.21 (1.09-1.34)	0.239	67.2	0.006	0.73 (0.62-0.85)	0.114
	LMIC | |	1	135/285	180/295	NA	1.000	1.52 (1.17-1.97)		NA	1.000	1.16 (0.82-1.64)	
Person-years	Actual	6	1230/2334	1476/2599	49.5	0.078	1.25 (1.11-1.41)	0.841	32.2	0.195	0.68 (0.59-0.79)	0.051
	Estimated	2	1719/3799	2294/4484	81.9	0.019	1.26 (0.91-1.74)		52.0	0.149	0.96 (0.75-1.22)	
Death Registries	Yes	4	1367/2848	1760/3324	56.7	0.055	1.29 (1.12-1.48)	0.501	8.9	0.349	0.72 (0.62-0.83)	0.700
	No	4	1585/3285	2010/3759	64.4	0.060	1.19 (0.98-1.44)		79.9	0.002	0.79 (0.59-1.05)	
Age difference§	≤ 4.5 years	1	1095/2049	1296/2304	NA	1.000	1.09 (0.98-1.20)	0.261	NA	1.000	0.88 (0.80-0.98)	0.474
	> 4.5 years	7	1854/4084	2474/4779	52.7	0.048	1.28 (1.14-1.45)		60.4	0.019	0.73 (0.61-0.88)	
Severity instrument	NIHSS	3	539/1118	761/1335	0.0	0.518	1.35 (1.17-1.55)	0.117	39.2	0.193	0.73 (0.56-0.96)	0.307
	Barthel	1	135/285	180/295	NA	1.000	1.52 (1.17-1.97)		NA	1.000	1.16 (0.82-1.64)	
	Others#	4	2275/4730	2829/5453	46.6	0.132	1.14 (1.02-1.26)		78.6	0.003	0.72 (0.58-0.89)	
SAH data	Yes	7	2863/5964	3637/6875	54.0	0.042	1.21 (1.10-1.34)	0.247	72.2	0.001	0.74 (0.62-0.88)	0.370
	No	1	86/169	133/208	NA	1.000	1.57 (1.14-2.15)		NA	1.000	1.01 (0.65-1.57)	
Sample size	≤1000	3	358/738	523/907	54.4	0.111	1.36 (1.08-1.72)	0.347	85.2	0.001	0.83 (0.48-1.43)	0.614
	>1000	5	2591/5395	3247/6176	53.6	0.071	1.19 (1.07-1.33)		56.1	0.058	0.75 (0.65-0.87)	
Participant-level characteristics‡												
Stroke type	IS	8	226/4949	2782/5546	35.3	0.147	1.21 (1.11-1.32)	Ref	48.7	0.058	0.88 (0.82-0.94)	Ref

Variables of interest		No of studies	No of death (n/N)		Unadjusted				Adjusted*			
			Men	Women	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$	I^2 (%)	P^H	MRR(95% CI)	$P^{sub-group}$
	ICH	8	450/770	526/840	61.1	0.012	1.27 (0.94-1.70)	0.529	63.4	0.008	1.01 (0.85-1.19)	0.722
	SAH	7	77/186	125/279	25.1	0.237	1.14 (0.73-1.76)	0.873	56.3	0.033	1.04 (0.68-1.57)	0.746
	Undetermined	8	158/228	337/418	35.8	0.143	1.51 (1.05-2.16)	0.397	45.2	0.078	1.02 (0.77-1.35)	0.150
Age group	≤65	8	394/1605	242/1131	41.9	0.099	0.90 (0.70-1.15)	Ref	-			
	>65-75	8	1939/3786	2084/4188	33.7	0.159	0.98 (0.89-1.08)	0.917	-			
	>75	8	616/742	1444/1764	36.9	0.134	1.09 (0.90-1.30)	0.055	-			

P^H, P-value of heterogeneity; $P^{sub-group}$, P-value for subgroup analysis; Ref, reference group; NA, not applicable; IS, Ischaemic stroke; ICH, Intracerebral haemorrhage; SAH, Subarachnoid haemorrhage; Barthel, Barthel index (at onset), NIHSS, National Institutes of Health Stroke Scale; MRR (95% CI), Mortality rate ratio (95% confidence interval) between women and men; HIC, High-income country; LMIC, Low- and middle-income country.

* MRR adjusted for actual confounders, but estimates for stroke type adjusted for age only; † estimates were performed using two-stage method analysis; ‡ estimates were performed using multivariate random-effect meta-analyses; § indicates difference in median age at onset between women and men; | | low- and middle-income country (LMIC) group included studies conducted in Martinique; # Other instruments including Glasgow coma scale and loss of consciousness

3.7 Supplemental Methods and Results

3.7.1 Supplemental Methods

Statistical analyses

Potential sources of heterogeneity: Study-level analysis

In these analyses, we calculated separate pooled effect estimates of sex differences in long-term mortality (13 studies at 1 year and 8 studies at 5 years) for models both unadjusted and adjusted for actual confounding factors, when appropriate.

Meta-regression of continuous variables of interest included: geographic latitude, proportion of women, proportion of hospital admission, mid-point of study year (e.g. a study ranging from 1987 to 2012, the mid-point was 1999), Global Gender Gap Index and years of potential life lost. Gender inequality may contribute to sex differences in long-term outcome of stroke when women receive less stroke care than men. We investigate the role of gender inequality in sex disparities in long-term mortality using the Global Gender Gap Index[232] (1-135) ranging from 4th in Sweden to 82nd in Brazil. It is possible that the magnitude of sex disparities may differ by differences in population-based life expectancy.[233] We examined whether years of potential life lost (YPLL) account for any heterogeneity of sex difference in mortality across studies. Ratio of years of potential life lost (YPLL) to life expectancy for women-to-men to follow-up (1-year or 5-year) in each study were estimated. The country-specific life expectancies were taken from World Bank data.[234] YPLL was measured by individual data from subtracting the person's age from their life expectancy at the year of outcome assessment.

Meta-regression of categorical variables of interest included: geographic region, mean age difference between women and men (≤4.5 years, >4.5 years), severity instruments, linkage to National Death Registries, availability of person-years data (actual data and imputed data), sample size (small sample size < 250[31] may affect the results), country income group (low- and middle-income countries (Martinique, Joinville and Matão) and high-income country), and availability of subarachnoid haemorrhage (SAH) type. Of note, we examined the role of availability of SAH cases because of the lack of these data in studies from Orebro and Tartu.

Patient-level analysis

To further examine the robustness of our findings we also tested interaction effects using the single pooled individual participant data dataset. We used multivariate random-effects meta-analysis[211] using the pooled IPD to assess the influence of participant-level characteristics on the sex differences in long-term mortality of. Vaartjes et al. have previously shown that sex difference in long-term mortality of stroke may differ by age group and stroke type.[97] There was considerable variation in

the year when stroke occurred from 1987 to 2013, and so we examined whether year of stroke occurrence influenced the sex difference in mortality in 1 year and 5 years post-stroke. In this data, we assessed the interaction between sex and participant-level covariates (stroke type, age at stroke onset and the year of stroke occurrence) by again testing the statistical significance of the sex × covariate product terms. In these analyses, we calculated separate pooled effect estimates of sex differences in 1-year mortality (13 studies) and in 5-year mortality (8 studies) in both unadjusted and adjusted for age, when appropriate.

Sensitivity analyses

Sensitivity analyses were used to examine the effect of the multiple imputation (m=50 imputations), early deaths after stroke and, in a subset of studies, stroke management on the results. The effect of imputation was examined by comparing crude and adjusted MRR between the complete-case and imputed datasets. The influence of death early after stroke on the sex difference in long-term mortality was examined by excluding deaths occurring at <1, <3 and <6 months after stroke. In the subset of studies with data on in-hospital management, we repeated the analyses among hospitalised patients with the addition of treatment or management variables.

Missing data and multiple imputation

For studies without person years, sex-specific person-years were estimated based on the distribution of available data (i.e. the nine remaining studies) using multiple imputation by chained equations[206] (m=50 imputations). The influence of imputed person-years on the pooled estimates was examined below in 'Potential sources of heterogeneity'.

Multiple imputation using chained equation[206] (m=50 imputation) was also used to impute covariates where the fully adjusted model had missing data on confounding factors for more than 20% of cases. The effect of imputation was examined by comparing crude and adjusted mortality rate ratio (MRR) between the complete-case and imputed datasets. The missing values of all covariates such as severity, co-morbidities were imputed by chained equations with 50 imputations based on all remaining completed variables in the dataset.

We then examined whether the exclusion of those with missing data on confounding factors influenced our pooled results by comparing the sex differences in mortality for complete-case analyses and imputed analyses.

Sex difference in mortality rate ratio excluding early deaths

To investigate the role of timing of death, we repeated Poisson modelling with the similar approach in forementioned method (see main text 'Statistical analysis') to estimate the sex difference in long-term mortality of stroke excluding early deaths occurring at <1, <3 and <6 months after stroke. These sensitivity analyses were then compared to the main findings.

Analyses among hospitalised participants

In the subset of studies with data on in-hospital management, we repeated the analyses among hospitalised patients with the addition of treatment or management variables including admission medication and discharge medication, in-hospital investigation and surgical interventions.

Analyses of admission medications including antihypertensives, antiplatelets and anticoagulants, neuroimaging and ECG were performed among all hospitalised patients irrespective of stroke type. However, analyses of admission thrombolysis, discharge antiplatelets, discharge anticoagulants, carotid investigation, holter monitor, echocardiography and carotid endarterectomy were examined for ischaemic stroke patients only. Analyses of coiling or clipping were performed only for those who suffered haemorrhagic strokes.

The two-stage method of analysis reported in the main text was then repeated among hospitalised patients to quantify the magnitude of crude and adjusted differences in long-term mortality with confounders not related to treatment. In the relevant subgroups specified above, we examined whether any treatment or management factors that showed a sex difference were confounders of the association between sex and mortality. We then examined whether the exclusion of those with treatment or management variables influenced our pooled results.

3.7.2 Supplemental Results

Missing data and multiple imputation

Long-term outcome data were very complete (**Appendix A**: **Supplemental Table A-7a**). Death data of seven studies were linked to National Death Registries. Studies in which cases were followed-up by study staff had low losses to follow-up. These losses were reported from original papers in L'Aquila, Auckland and Porto. Of note, 7 cases lost to follow-up in Arcadia were not included in the analyses.

Missing confounder data reduces the number of cases in the fully adjusted models within each study up to 26% (**Supplemental Table A-7a**). Only the study from Melbourne, with the greatest amount of missing data on confounders (>20%) both at 1 year and 5 years after stroke, was required to have imputation of missing confounder information. In Melbourne data, results from imputed models showed the same factors contributing to the sex difference in both 1-year and 5-year mortality after stroke compared to complete-case analysis. After accounting for these confounding factors, compared to complete-case analysis (main **Figures 3-2** and **3-3**), the trend of the sex difference after imputation remained unchanged (supplementary table 9b) with the RR being 0.89 at 1 year (vs 0.76, main **Figure 3-2**) and 0.85 at 5 years (vs 0.69, main **Figure 3-3**).

In the analysis using multiple imputation, inclusion of imputed data for the Melbourne study had no impact on the estimated relative sex differences in mortality at 1 or 5 years, in both unadjusted and adjusted estimates (**Supplemental Table A-7b**).

Sex difference in mortality rate ratio excluding early deaths (1 month, 3 months and 6 months)

1-year analysis

The magnitude of sex difference in crude 1-year mortality after stroke remained the same when excluding deaths occurring within the first month (MRR 1.29 95% CI 1.11, 1.48 vs 1.35 95% CI 1.24, 1.47) but largely attenuated when excluding deaths within 6 months after stroke (MRR 1.14 95%CI 0.92-1.40; supplementary table 10). After accounting for significant confounders, the sex differences were reversed with MRR ranging from 0.81 to 0.84, this being closely similar to the figure of 0.81 in main analyses that included all deaths (main **Figure 3-2**).

5-year analysis

The magnitude of sex difference in crude 5-year mortality after stroke attenuated but remained significant when excluding deaths occurring within the first month (MRR 1.15 95% CI 1.02, 1.30 vs 1.24 95% CI 1.12, 1.38) but was no longer significant after excluding deaths within 6 months after stroke (MRR 1.07 95% CI 0.92, 1.25; **Supplemental Table A-8**). After accounting for significant confounders, the sex differences were reversed with MRR ranging between 0.77 and 0.78, these being closely similar to the figure of 0.76 in the main analyses that included all deaths (main **Figure 3-3**).

Hospitalised analysis

Sex differences in treatment and management of stroke

There was little evidence of sex difference in admission medication including antihypertensives (1/3 studies), antiplatelet agents (0/4 studies), anticoagulants (2/4 studies), thrombolysis (0/4 studies) and discharge medication including antihypertensives (0/4 studies), antiplatelet agents (0/5 studies), and anticoagulants (0/4 studies; **Supplemental Table A-9**).

There were no sex differences in the proportion of investigations undertaken including ECG (9 studies), neuroimaging (12 studies), and holter monitor (3 studies) investigations among studies that had these data. In very few studies women underwent fewer echocardiography procedures (3/7 studies) and carotid investigations (4/9 studies), or carotid endarterectomy (1/2 studies). No difference in surgical intervention between men and women was found (**Supplemental Table A-9**).

Sex differences in 1-year mortality and 5-year mortality among hospitalised patients

The unadjusted difference in mortality between men and women was similar for hospitalised patients and all participants. Among the 95·8% (14350/14972) of subjects who were admitted at 1 year and 99·3% (11287/11368) at 5 years, women were more likely than men to be deceased at 1 year (excessive mortality 33% [95% CI 22%, 44%]) and 5 years (excessive mortality 21% [95% CI 10%, 33%]). The confounding factors contributing to these differences were similar to the main findings (main **Table 3-2**).

Subgroup analyses among patients hospitalised with ischaemic stroke

With the exception of carotid investigations in Joinville, none of the potential confounding factors confounded the association between sex and mortality in hospitalised patients (**Supplemental Table A-10**). In Joinville, adjustment for carotid investigations reduced the 1-year MRR by 59% among hospitalised cases. The pooled estimates of the MRR for women compared to men, including the new estimate for Joinville, remained virtually unchanged (**Supplemental Table A-11**).

Chapter 4: Sex differences in long-term functional outcome and participation restriction after stroke in the INternational STRoke oUtComes sTudy (INSTRUCT)

4.1 Preface

This thesis chapter has been published as a paper in the *Neurology* (see **Appendix I**).

Phan HT, Blizzard CL, Thrift AG, Cadilhac D, Sturm J, Heeley E, Konstantinos V, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Para V, Bejot Y, Cabral N, Carolei A, Sacco S, Chausson N, Olindo S, Rothwell P, Silva C, Correia M, Magalhães R, Appelros P, Korv J, Vibo R, Minelli C, Reeves M, Otahal P, Gall S. Factors contributing to sex differences in functional outcomes and participation after stroke. *Neurology*. 2018. (Journal IF ~ 8.3; citation: 2). https://doi.org/10.1212/WNL.0000000000005602.

This paper was also accompanied by an editorial noting its novelty, significance and implications for improving long-term outcome after stroke (*see Editorial by Andrew and Srikanth:* https://doi.org/10.1212/WNL.0000000000005591).

4.7 Supplemental Methods and Results

4.7.1 Supplemental Methods

Statistical analysis

Because covariates were not measured uniformly between studies, we could not harmonise and adjust for the same set of covariates. Hence, a two-stage analysis method[204] for the analysis of pooled data was used. For the first stage of analysis, study-specific models for functional outcomes were built using log-binomial regression to estimate the relative risk (RR) of poor outcome for women compared to men at 1 year (10 studies) and 5 years (7 studies) after stroke. Of note, follow-up data on functional outcomes available at 4 years (for Tartu) or 7 years (for Porto) were included in 5-year analyses together with outcome data at 5 years of the other four studies. Poor outcome was defined as BI <20 (Melbourne and Matão) and mRS >2 (remaining studies). The 100-point version of BI used in the Matão study was rescaled to be the same as the other studies.

Two of the cohorts (Melbourne and Auckland) included assessment of participation at 5 years after stroke using the London Handicap Scale (LHS).[240] The dimensions of the LHS include: orientation, physical independence, mobility, occupation, social interaction and economic self-efficiency. The overall LHS score is obtained by applying weights to each subdomain score (0 [worst] to 6 [no disadvantage]), summing them, and adding a constant; it ranges from 0 (very disadvantaged) to 100 (not disadvantaged). For analyses of participation restriction (or handicap), study-specific multivariable linear regression, with Box-Cox transformation of the outcome to remove skewness, was used to compare the mean difference of LHS total scores (0-100) for women and men (2 studies, Melbourne and Auckland). Back-transformed estimates are presented. Because of causal relationship between LHS and functional outcome such as BI,[260] we did not include long-term functional outcome in analyses of participation restriction.

Within each study, we then assessed the role of the covariates in the association between sex and each outcome using purposeful model building.[207] Variables were entered into the model only if they met for all our 4 criteria (being missing <20% of cases, associated with sex with $p<0{\cdot}1$, associated with the outcome with $p<0.1$, and the inclusion of the covariate in a model with only sex changed the magnitude of the sex coefficient by ≥10% [unadjusted β – adjusted β)/ unadjusted β *100]).[24]

The model-building process started with separate analyses for each variable. Adjustment was then made for all confounders in multivariable analyses but with age, stroke severity and pre–stroke function (where available), forced into a final fully adjusted model. Within each study, the modifying effect of a covariate on the sex difference was assessed by a test of the statistical significance of the coefficient of a sex × covariate product term.

For the second stage of the analysis, both unadjusted and adjusted study-specific estimates were pooled in separate meta-analyses, so that the pooled values could be compared to determine the effect of adjustment. Heterogeneity was evaluated using I^2 statistics with the Mantel-Haenszel approach.

Sensitivity analyses

Potential sources of heterogeneity: Study-level characteristics

Potential sources of heterogeneity were assessed among variables of study-level characteristics (e.g. geographic region, income group and instrument of functional outcome). Between-study interactions between sex and study-level characteristics were assessed by meta-regression. In these analyses, we calculated separate pooled effect estimates of sex differences in long-term functional outcome (10 studies at 1 year and 7 studies at 5 years) for models both unadjusted and adjusted for actual confounding factors, when appropriate.
Meta-regression of continuous variables (n=6 variables) of interest included: geographic latitude, proportion of women, proportion of hospital admission, mid-point of study year (e.g. in the Oxford study, year of stroke ranged from 2002 to 2013, and the mid-point was 2008), Global Gender Gap Index and years of potential life lost. Gender inequality may contribute to sex differences in long-term outcome of stroke when women receive less stroke care than men. We investigated the role of gender inequality in sex disparities in long-term functional outcome using the Global Gender Gap Index[232] (1-135) ranging from 4th in Sweden to 82nd in Brazil. It is possible that the magnitude of sex disparities may differ by differences in population-based life expectancy.[233] We examined whether years of potential life lost (YPLL) account for any heterogeneity of sex difference in functional outcome across studies. Ratio of year of potential life lost (YPLL) to life expectancy for women-to-men to follow-up (1-year or 5-year) in each study was estimated. The country-specific life expectancies were obtained from World Bank data.[234] YPLL was measured individually by subtracting the person's age from their life expectancy at the year of outcome assessment.

Other sensitivity analyses

Analyses in a single IPD dataset

There were three covariates measured consistently in all studies: year of stroke occurrence (ranged from 1993 to 2014), age at stroke onset and stroke type. To further test the robustness of our findings, we used a single-stage meta-analysis pooling all IPD datasets[210] to examine whether these factors modified the sex-effect on poor functional outcome at 1 year (10 studies) and 5 years (7 studies) after stroke. We chose $p \leq 0.10$ as the cut-off for statistical significance of the interaction (sex × covariate product term) because this value is commonly accepted in the literature for detecting interactions.[113]

Missing data and sensitivity analyses

We undertook a wide range of sensitivity analyses to assess other potential bias. For studies with >20% missing data of long-term functional outcomes, participation or covariates, multiple imputation using chained equations (n=50 imputations) combined with Inverse-Probability Weighting[241] was performed and compared with results from complete-case analyses. These sensitivity analyse were based on the assumption that the data were missing at random. The missing values of outcomes and all covariates, where necessary, such as severity and co-morbidities were imputed based on all remaining completed variables in the dataset. We then examined whether the exclusion of those with a high rate of missing data on outcomes and confounding factors influenced our pooled results by comparing the sex differences in functional outcomes for complete-case analysis and imputed analysis with unadjusted and fully-adjusted models.

We also performed sensitivity analysis by replacing missing observations on functional outcome with extreme values of 0 or 1 and compared with results from complete-case analyses.[261] These further analyses were based on worst-case scenario (all missing cases had poorest possible functional outcome after stroke). To show the range of results that might be possible. We had added also a best-case scenario (all missing cases had the best possible functional outcome).

Furthermore, we considered removing studies at risk of bias (high proportion of patients lost to follow-up) in sensitivity analysis. We compared the pooled effect size estimates between models that included and excluded these studies.

Analyses among survivors who were hospitalised at stroke onset

Analyses among hospitalised patients were carried out to determine whether there were sex differences in treatment and management, and whether any differences in these variables influenced the sex differences in outcome. We used χ^2 test or Fisher's exact test, as appropriate, to examine whether there were sex differences in admission medication and discharge medication, in-hospital investigation and surgical interventions. Analyses of admission medications including antihypertensive agents, antiplatelet therapies and anticoagulation therapies, neuroimaging and ECG were performed among all hospitalised patients irrespective of stroke type. However, analyses of admission thrombolysis, antiplatelet agents at discharge, anticoagulation therapies at discharge, carotid investigation, holter monitor, echocardiography, carotid endarterectomy were examined for patients with ischaemic stroke only. Analyses of coiling or clipping were performed only for those who suffered haemorrhagic strokes.

The two-stage method of analysis reported in the main text was then repeated among hospitalised patients to quantify the magnitude of crude and adjusted differences in long-term functional outcome with confounders that were not related to treatment. Then, in the relevant subgroups specified above, we examined whether any treatment or management factors that showed a sex difference were confounders of the association between sex and functional outcome.

Other sensitivity analyses

For functional outcomes, due to some evidence proposing an ordinal model approach of mRS,[262] we also considered sex difference in poor outcomes at full ordinal scale among studies that had these data. Ordinal regression with the continuation-ratio approach[263] was used to calculate the effect size of the sex difference in functional outcomes after stroke with mRS data, and was then compared to the dichotomous analysis.

Authors of some previous studies have reported a cut-off of 95 for BI to define poor outcome (100-point version).[264] Therefore, among studies with BI data, alternative cut-off points for poor outcome (BI <95 for Matão or <19 for Melbourne) were compared with the main analyses (BI <100 for Matão or <20 for Melbourne). Analyses among hospitalised patients were carried out to determine whether there were sex differences in treatment and management of stroke, and whether any differences influenced the differences in functional outcome. We quantified the magnitude of unadjusted and adjusted differences in long-term functional outcomes with the addition of treatment or management variables.

For participation outcome, we compared the level of participation restriction (score 0-6 with higher categories denoting more severe disadvantage) in each of the six dimensions. Because there were some extreme values of higher level of participation restriction, we collapsed the LHS sub-domain scores into two levels including less disadvantage (categories 1-2) and disadvantage (categories 3-6).

4.7.2 Supplemental Results

Sex difference in 5-year functional outcome after stroke

Analysis of 5-year functional outcome included 2,084 cases (94% of available cases) due to missing data of some confounders. At 5 years after stroke, women had a 31% higher risk of poor functional outcome in unadjusted analyses (**Figure 4-2**, top panel). There was no evidence of heterogeneity in sex difference in long-term functional outcome of stroke at 5 years (I^2=0.0, p=0.476). Contributors of the sex difference included baseline age (6/7 studies), severity (2/7 studies) and pre-stroke dependency (4/5 studies). Separate adjustment by inclusion of individual covariates changed the coefficient for sex difference substantially, age alone explained 45% of the sex difference (pooled age-adjusted RR 1.16 [95% CI 1.03, 1.30] with I^2=0.0, p=0.710; **Appendix B: Supplemental Table B-4a**). The effect was also reduced with separate adjustment for stroke severity (17%) and pre-stroke dependency (28%; **Supplemental Table B-4a**). No interaction between sex and any of these factors in the 5-year functional outcome after stroke was found with the exception from Oxford study (**Supplemental Table B-4b;** with the excessive risk of worse functional outcome for women was stronger in those who were independent before stroke (unadjusted RR 1.61 [95% CI 1.21, 2.15], adjusted RR 1.37 [1.01, 1.72]) compared to participants who were dependent before stroke (unadjusted RR 0.90 [0.77, 1.04], adjusted RR 0.87 [0.71, 1.06]; for these interactions, p<0.05). There was no evidence that socioeconomic status, cardiovascular risk factors, medical comorbidities, post-stroke recurrence and depression were confounders of the association between sex and poor

functional outcome (**Supplemental Table B-10**). The pooled adjusted RR was 1.05 (95% CI 0.94, 1.18) with no evidence of heterogeneity (I^2 = 0.0, p = 0.870). Meta-regression did not identify any sources for the heterogeneity observed in 5-year crude or adjusted models (**Supplemental Table B-11**).

In further analyses of the IPD data, none of the 3 participant-level characteristics of age, stroke type and the year of stroke occurrence were significant sources of between-study variation (**Supplemental Table B-5b**).

Sensitivity analyses

Missing data and imputation

1-year analysis

As shown in **Supplemental Table B-7**, among who survived to 1 year after stroke, information on potential confounding factors were missing in up to 16% of participants within studies. However, functional outcome data to 1 year after stroke were less complete in three studies (Melbourne, Perth and Tartu) with missing data up to 70%. Removing Perth, which had the greatest missing 1-year outcome data did not affect the results (**Supplemental Table B-6**). We found no difference in proportion of women and age at stroke onset between those who were assessed in the long-term and those lost to follow-up (**Supplemental Table B-8a**).

As shown in **Supplemental Table B-9**, though the relative risks of imputed 1-year functional outcome for those studies with >20% lost to follow-up (Barthel Index for study from Melbourne and mRS for study from Perth and Tartu) attenuated the sex difference, greatest in study from Perth, the pooled estimates remained mostly the same compared to complete-case analyses. Pooled crude 1-year RR for poorer functional outcome slightly altered from 1.32 to 1.31 in crude analysis and remained 1.08 after fully adjustment for confounders.

5-year analysis

As shown in **Supplemental Table B-7**, among those who survived to 5 years after stroke, information on potential confounding factors were missing in up to 20% of participants within studies. Functional outcome data to 5 year after stroke were less complete in two studies (Melbourne and Auckland) with missing data up to 65.6%. Removing Auckland that had the greatest missing 5-year outcome data (**Supplemental Table B-6**) did not affect results. We found no difference in proportion of women between those who were assessed in the long-term and those lost to follow-up (**Supplemental Table B-8b**). However, who lost to follow-up were younger than those were assessed functional outcome at 5 years after stroke.

As shown in **Supplemental Table B-9**, relative risks of imputed 5-year functional outcome for those studies with >20% lost to follow-up (Barthel Index for study from Melbourne and mRS for study from Auckland) showed a slightly change. The pooled estimates were also similar to the complete-case analyses. Pooled crude 5-year RR for

poorer functional outcome slightly attenuated from 1.31 to 1.26 in crude analysis and from 1.05 to 1.02 after fully adjustment for confounders.

Other sensitivity analyses

1-year analysis

Using an alternative cut point for the Barthel Index (Melbourne and Matão) did not change the summary estimates of sex difference in functional outcomes at 1 year after stroke. An ordinal regression model of mRS categorised into 3 levels (0-1, 2-3 and 4-5) supported the results with a dichotomous outcome at 1 year (**Supplemental Figure B-1**).

5-year analysis

Using an alternative cut point for the Barthel Index (Melbourne) did not change the summary estimates of sex difference in functional outcomes at 5 years after stroke. An ordinal regression model of mRS categorised into 3 levels (0-1, 2-3 and 4-5) supported the results with a dichotomous outcome at 5 years after stroke (**Supplemental Figure B-2**).

Hospitalised analysis

There was little evidence of sex differences in acute treatment and management of stroke among survivors at 1 year (**Supplemental Table B-12**) and 5 years (**Table B-13**) after stroke. Generally, the unadjusted differences in functional outcome between men and women in the long term after stroke were the same for hospitalised patients only as for all participants (hospitalised and non-hospitalised). Among those hospitalised, women often suffered poorer functional outcomes at 1 year (32%; **Supplemental Figure B-3**) and 5 years (34%; **Supplemental Figure B-4**). In study specific models, factors contributed to the difference between men and women were similar to that depicted in **Table 4-2** (e.g. age, severity, pre-stroke dependency) without any additional factors of treatment and management of stroke.

Chapter 5: Sex differences in long-term health-related quality of life after stroke in the INternational STroke oUtComes sTudy (INSTRUCT)

5.1 Preface

At the time of submission of this thesis, the contents of this chapter have been circulated to co-authors in preparation for submission for publication.

Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, Heeley E, Otahal P, Rothwell P, Anderson C, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Gall SL. Sex differences in long-term health-related quality of life after stroke in the INternational STroke oUtComes sTudy (INSTRUCT).

5.2 Abstract

Background: Women are reported to have poorer health-related quality of life (HRQoL) after stroke than men, but the reasons why are uncertain. We aimed to investigate sex differences in HRQoL up to 5 years after stroke and identify factors contributing to these differences.

Methods: Individual participant data on 9,109 first-ever strokes (1993-2014) were obtained from 10 high-quality incidence studies from Australasia, Europe, South America, and the Caribbean. Study factors included socio-demographics, pre-stroke dependency, stroke-related factors (e.g. stroke severity), comorbidities, post-stroke

depression, and functional status. HRQoL utility scores were calculated from the EQ5D, SF6D, and AQoL at 1 year (3 studies; n=1,210) and 5 years (3 studies; n=1,057) after stroke. EQ5D utility scores were also mapped from the modified Rankin Scale (mRS) at 1 year (8 studies; n=4,303) and 5 years (6 studies; n=2,208). Quantile regression was used to estimate the median differences (MD) in HRQoL utility scores for women compared to men with adjustment for covariates/confounding factors. Study-specific unadjusted and adjusted MDs were then combined into pooled estimates using random-effect meta-analysis.

Findings: Women (average age: 73 vs men 70 years) had lower pooled mean utility scores than men (1-year $MD_{unadjusted}$ -0.147, 95% CI -0.258, -0.036; 5-year $MD_{unadjusted}$ -0.090, 95% CI -0.119, -0.062). These differences were attenuated after adjustment for age, stroke severity, pre-stroke dependency, and depression (1-year pooled $MD_{adjusted}$ -0.067, 95% CI -0.111, -0.022; 5-year $MD_{adjusted}$ -0.085, 95% CI -0.135, -0.034). Similar trends were observed for mapped EQ5D utility scores (1 year pooled $MD_{unadjusted}$ -0.043, 95% CI -0.064, -0.021; $MD_{adjusted}$ -0.014, 95% CI -0.023, -0.005; 5-year $MD_{unadjusted}$ -0.040, 95% CI -0.075, -0.005; $MD_{adjusted}$ -0.020, 95% CI -0.044, 0.004).

Conclusion: Poorer HRQoL was consistently observed in women after stroke. It was mostly attributable to their advanced age, more severe strokes, pre-stroke dependency, and post-stroke depression, suggesting targets to reduce the differences.

5.3 Introduction

The greater burden of stroke in women than in men has recently been recognised as a major concern worldwide.[235,256] Women generally have a poorer health-related quality of life (HRQoL) than men, both in the short and long term after stroke.[23,24] Despite the increased interest in sex differences, the reasons for worse HRQoL in women have not been adequately investigated. HRQoL is defined as an assessment of how the individual's well-being may be affected over time by a health condition such as disease, disability, or disorder.[73] HRQOL has become an important component of health surveillance and is generally considered a valid indicator of service needs and intervention outcomes.

Existing studies of sex differences in HRQoL after stroke have several limitations.[23,24] The studies were mainly focused on short-term outcomes up to 6 months after stroke.[24] Many investigators did not report sex-specific findings, or used modelling that was not focused on the sex difference. The association between sex and outcomes in the studies was usually reported as an incidental finding. Of a small number of studies specifically designed to examine sex differences, most were either based in the hospitals/convenience samples or restricted to a specific type of stroke or certain age groups. This is problematic as selection bias may adversely affect conclusions.[26] By contrast, among several ‘ideal’ population-based stroke incidence studies[236] that are the most generalisable and ideal to examine sex differences,[28,30,94] very few had aHRQoL assessment or were analysed to assess for sex differences. There are inconsistent findings regarding the factors associated with sex difference in HRQoL because of variation in outcome measurement and adjustment for different

covariates.[24] In the most recent update, only two out of 13 studies on sex differences in HRQoL published since 2007 were designed to examine the sex differences, and none of these were population-based studies.[23]

The aim of this study was to quantify the differences between men and women in HRQoL at 1 and 5 years after stroke and identify factors contributing to any observed sex differences. We used individual participant data from 'ideal' incidence stroke studies conducted in different countries.

5.4 **Method**

The INternational STroke OUtComes STudy (INSTRUCT) is an international collaboration whereby we have pooled individual patient data after first-ever stroke. The INSTRUCT includes 13 studies from Australasia, Europe, South America and the Caribbean (1987 and 2014; n=16,964 incident strokes at baseline) that adhered to the criteria for 'ideal' population-based stroke incidence studies (**Chapter 2**). This project was registered in the PROSPERO (CRD42016036723) and approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0014861). All the participating studies had approval from their respective local Ethics Committees. The 13 studies included in INSTRUCT represented 59% of the 22 potentially eligible studies identified through our systematic search. More details of the study selection process are provided in **Chapter 2**. Ten out of the 13 studies were included in the analyses of sex differences in long-term HRQoL for this current study (Table 2-7).

5.4.1 Outcome measurements

In the 10 studies, participants of eight studies were followed up with face-to-face interviews conducted at 1 and 5 years after stroke, while in the remaining two studies (Joinville, Tartu), mail or telephone interviews were used (**Chapter 2**).[265]

Of the 10 studies, four had measures of HRQoL among survivors after stroke (Table 2-7; Oxford, Perth, Melbourne, and Auckland). However, the measures were available for three studies at 1 year (Oxford, Perth, and Melbourne) and for three studies at 5 years (Oxford, Auckland, and Melbourne). Three instruments were used to assess the HRQoL in the long term after stroke including the European Quality of Life–5 Dimensions (EQ5D),[194] the Assessment of Quality of Life (AQoL),[195] and the Short Form–36 questionnaire (SF36)[266]. In the Oxford study, HRQoL was assessed using the EQ5D instrument. For each of the five dimensions of the EQ-5D (including mobility, self-care, usual activities, depression/anxiety, and pain), there are three response categories: no problem, some/moderate, and extreme problem. In the Melbourne (Australia) study, the AQoL was used. The AQoL has five dimensions comprising illness, independent living, social relationships, physical senses, and psychological wellbeing with four response levels for each domain (from needing no help to requiring daily help). The SF36 was used to assess HRQoL among stroke survivors in the Perth (Australia) and Auckland (New Zealand) studies. The SF36 instrument, validated for use among patients with stroke, covers both physical and mental health with eight sub-dimensions.[267]

In additional analyses data from studies with the modified Rankin scale (mRS; measurement of functional outcome) at 1 year (8 studies: Oxford, Joinville, Arcadia,

Perth, Orebro, Martinique, Porto, and Tartu) or 5 years after stroke (6 studies: Oxford, Joinville, Martinique, Porto, Auckland, and Tartu) was assessed whereby the mRS was mapped to European Quality of Life–5 Dimensions (EQ5D) utility scores using the published algorithm.[268]

5.4.2 Study factors

We included covariates that we hypothesised from our previous studies[84,94] that might explain differences in outcomes between men and women. These included socio-demographics (e.g. *age, marital status, institutional residence*), pre-stroke health (e.g. *pre-stroke dependence*) and comorbidities (e.g. *hypertension, atrial fibrillation, smoking, alcohol consumption*), stroke-related factors (*stroke type, severity*), treatment and management (*admission and discharge medication, in-hospital investigation and surgical interventions*) and post-stroke factors (e.g. *depression, functional outcome*). A summary of the potential confounding factors available in each study was described earlier in **Chapter 2**: section **2.5**.

5.4.3 Statistical analysis

All the data were analysed in Stata 12.1 (StataCorp Texas, 2011).[269] All two-tailed p-values ≤ 0.05 were considered statistically significant.

HRQoL utility scores were calculated from the three instruments (EQ5D, AQoL, and SF36) among survivors after stroke by summing the component scores and adding value sets from relevant general populations to create an overall score. The utility

score is a scale on which full health has a value of 1, while 0 indicates death and negative values indicate health states worse than death. The SF6D utility scores (Perth, Auckland) were estimated from the SF36 using the published algorithm for the United Kingdom (UK) population[270] given the lack of SF-6D preference weights for Australia or New Zealand (NZ).[271] The AQoL utility scores (Melbourne) were calculated based on the Australian population-based methods[195] while the EQ5D utility scores (Oxford) were derived from patient data using the available value sets for the UK population.[272] Among studies with mRS data, EQ5D utility scores were further mapped from the mRS categories (0-5) using the published algorithm.[268]

The measured and mapped utilities scores were analysed in separate models. Due to a lack of evidence on using mRS-based HRQoL after stroke, the mapped scores were only reported in sensitivity analyses to compare with our main analyses of measured HRQoL. Quantile regression was used to estimate the median difference for women compared to men in utility scores among survivors at 1 and 5 years after stroke. We used a two-stage analysis method[204] where study-specific models for sex difference in HRQoL were built in the first stage. Within each study, the role of the covariates as confounders[207] of the association between sex and HRQoL outcome were assessed (**Supplemental Methods**: **section 5.7**). Age, stroke severity, and pre-stroke dependency that are common predictors of HRQoL and associated with sex,[23,24] where possible, were forced into the final multivariable models accounting for all significant confounding factors. Given a high correlation between HRQoL and functional outcome,[273] we did not include long-term functional outcome in the final models to avoid over-adjustment bias. Further adjustment for this factor is reported in separate models.

In the second stage of the analysis, the effect estimates from unadjusted and multivariable-adjusted models were combined to create pooled estimates in separate random-effects meta-analyses. Statistical heterogeneity between studies was evaluated using I^2 statistics. The potential sources of heterogeneity were assessed among several variables of interest (**Supplemental Methods**: **section 5.7**) using meta-regression.[231]

We found substantial disparities in the number of health states (EQ5D-3L: 243, SF-6D: 18,000, and AQoL: 1.07 billion health states)[274,275] across instruments and their definitions of the minimum clinically important difference.[276,277] The comparability of the study populations with measured HRQoL was undertaken to see whether the sex differences in utility scores might be clinically meaningful or not. In these analyses, the differences between men and women at 0.06 for AQoL,[276] 0.08-0.12 for EQ5D,[277] and 0.03-0.08 for SF6D[277] were considered as clinically relevant.

For the studies with more than 20% missing data on long-term outcomes, multiple imputation using chained equations (n=50 imputations) combined with Inverse-Probability Weighting[241] was performed to compare with results from complete-case analyses.

Subdomain analyses

Further, subdomain analyses among the included studies (Auckland and Perth: SF36; Melbourne: AQoL) were performed to determine the dimensions of HRQoL that affected women more often than men in the long-term after stroke.

Analyses of the comparison with general populations

We also examined whether the poorer HRQoL after stroke in women was due to stroke or other differences in the comparison between stroke and general populations.

For each study with measured HRQoL (EQ5D, AQoL, and SF-6D), mean (and standard deviation, SD) utility scores for stroke survivors were calculated within sex and different age groups (<55, 55-64, 65-74 and ≥75 years old). To examine the HRQoL loss caused by stroke when compared with the general population, we included those assessed with HRQoL after stroke at 1 or 5 years of follow-up (not including death). For each instrument, the corresponding reference scores in the general population were obtained from the current literature on UK norms for EQ5D,[278] and Australian norms for AQoL.[276] Due to a lack of published NZ reference scores for SF-6D, Australian norms for SF-6D were used as a surrogate.[271] We then calculated the nect mean difference scores between stroke and general populations within each age group, separately for men and women. The Perth study was excluded from these analyses due to the small sample size by age and sex strata.

5.5 **Results**

There were with 9,109 first-ever stroke registrants at baseline among the included 10 studies. HRQoL outcomes were assessed among 1,210 (63%) of 1,914 survivors at 1 year (3 studies) and 1,057 (58%) of 1,837 survivors at 5 years (3 studies) after stroke (**Table 5-1**). Further, the mapped EQ5D utility scores were available among 4,303 (78%) of 5,498 survivors at 1 year (8 studies) and 2,208 (70%) of 3,142 survivors at 5 years (6 studies).

Differences between women and men at the time of stroke and long-term follow-up

In analyses of baseline factors among survivors with 1-year HRQoL assessment, women were older (statistically significant difference in 3/3 studies; **Appendix C**: **Supplemental Table C-1**) and more dependent before stroke than men (3/3 studies; evaluated by the mRS or the Barthel Index). They also more often had a higher mean score of stroke severity than men although the sex difference was small. Men were often ever-smokers (3/3 studies) or alcohol consumers (2/3 studies). There was very little difference between men and women in comorbidities, acute stroke therapies and management (**Supplemental Table C-1**). Similar results were found in the comparison between sexes of the study factors among those assessed at 5 years within each cohort (**Supplemental Table C-2**).

Regarding post-stroke factors, women often had poorer functional outcomes assessed by the mRS or the Barthel Index (1 year: 3/3 studies; 5-year: 2/3 studies) than men. In the Melbourne study, women appeared to have more mood disorders (i.e., anxiety or depression) and take antidepressant medications at 5 years after stroke more frequently than their male counterparts (**Supplemental Tables C-1 and C-2**).

Among studies with HRQoL mapped scores (from the mRS), with the patient characteristics by sex being presented in our previous publication on functional outcome,[265] women were older, had greater pre-stroke dependency, and poorer functional outcomes at 1 and 5 years after stroke than men.

Sex difference in long-term HRQoL among survivors after stroke

Among three studies with measured HRQoL at 1 year, the sample for complete-case analysis was 1,116 (92% of available cases) because of missing data on some

confounding factors. In unadjusted analyses, women had significantly poorer median utility scores at 1 year after stroke (pooled median difference, $MD_{unadjusted}$ -0.147, 95% CI -0.258, -0.036). Study-specific unadjusted female:male MD varied from -0.069 (Oxford), -0.197 (Melbourne) to -0.210 (Perth; **Figure 5-1**, top). All the sex differences were statistically significant but were above only the clinically meaningful threshold in the Melbourne and Perth studies.

However, the differences were substantially attenuated (by 61.4%) after accounting for covariates (1-year pooled $MD_{adjusted}$ -0.067, 95% CI -0.111, -0.022; **Figure 5-1**, bottom). In study specific models, the significant confounding factors of the association between sex and HRQoL were identified: age (2/3 studies), stroke severity (1/3 studies), pre-stroke functional outcome (1/3 studies), and mood disorders (Melbourne study; **Table 5-2**). No factors of treatment and management of stroke accounted for the sex differences in 1-year HRQoL. Among the three studies, the adjusted female:male MD only remained clinically significant in the Perth study. Further adjustment for 1-year functional outcome removed the association between sex and HRQoL across the studies (**Table 5-2**). There were no statistical interactions between sex and covariates on the HRQoL scores.

Similar trends were found among 8 studies with mapped utility scores at 1 year, in which the pooled unadjusted female:male MD were -0.043, 95% CI -0.066; -0.021 and reduced to -0.011 (-0.023; -0.005; **Supplemental Figure C-1**) after adjustment for confounding factors. There was no statistical heterogeneity across the studies (I^2 =25.2%, p=0.228) in adjusted analyses.

For the 5-year analyses of measured HRQoL (n=3 studies), the sample for complete-case analysis was 927 (88% of available cases) because of missing data on some confounding factors. In unadjusted analyses, women had significantly poorer utility scores (5-year pooled $MD_{unadjusted}$ -0.090, 95% CI -0.119, -0.062). All the study-specific unadjusted female:male MDs were statistically and clinically significant (**Figure 5-2**, top).

The sex differences were slightly attenuated (by 5%; 5-year pooled $MD_{adjusted}$ -0.085, 95% CI -0.135, -0.034; **Figure 5-2**, bottom) and still significantly different in 2 out of 3 studies (Melbourne and Auckland) after adjustment. The major confounders were age (3/3 studies), stroke severity (2/3 studies), pre-stroke function (2/3 studies) and post-stroke mood disorders (1/2 studies; **Table 5-3**). No statistical interactions were observed between sex and covariates on 5-year HRQoL scores. Among the three studies, the adjusted female:male MD only remained clinically significant in the Melbourne and Auckland studies. Further adjustment for 5-year functional outcome removed the association between sex and HRQoL across the studies (**Table 5-3**).

Similar trends were observed among 6 studies with mapped utility scores from the mRS whereby 5-year unadjusted female:male MD were -0.040, 95% CI -0.075; -0.005 and reduced by half after adjustment for above-mentioned confounding factors ($MD_{adjusted}$ -0.020, 95% CI -0.044, 0.004; **Supplemental Figure C-2**).

The greatest loss to follow-up was observed in the study from Perth (1 year) and Auckland (5 years), but very few differences between completers and non-completers in baseline characteristics were identified (**Supplemental Tables C3 and C4**). Sensitivity analyses using the multiple imputation combined with inverse probability

weighting to account for missing data showed that our results were robust (**Supplemental Table C-5**).

Sex difference in sub-domain HRQoL scores among survivors

In the Melbourne study, women survivors of stroke had worse scores on three out of five AQoL domains, compared to men, including independent living (1 year), social relationships (1 and 5 years), and psychological well-being (1 and 5 years; **Supplemental Table C-6**). In the Auckland study, women had lower HRQoL at 5 years than men in SF-36 domains including physical functioning and mental health (**Supplemental Table C-7**). Generally, compared to men, women's advanced age, more severe strokes, and pre-stroke dependency contributed to their poorer physical health while the greater post-stroke mood disorders (Melbourne) in women contributed to their poorer mental health (**Supplemental Tables C-6 and C-7**).

Comparison between women and men in stroke and general populations

Generally, HRQoL loss due to stroke, indicated by net differences in utility scores between stroke and the relevant general population, was increased with advanced age for both sexes (**Supplemental Tables C-8a to C-10**). Men and women who survived after stroke had worse utility scores than those in the general population across age groups and the differences were well above clinically relevant thresholds. Statistically significant results were achieved more frequently in the analyses of 1-year outcome compared to analyses of 5-year outcome (**Supplemental Tables C-9b** and **C-10**).

As compared with the general population, the reduction in HRQoL among stroke survivors was generally more extreme in women than in men. However, the

magnitude of the sex difference varied among age groups and outcome instruments, and often below clinically relevant thresholds. In the analyses of AQoL utility scores (Melbourne), compared with the general population, the differences in HRQoL at 1 and 5 years between women and men survivors of stroke were greater for those aged <65 years than for older people (**Supplemental Table C-8a** and **C8-b**). The sex differences in SF6D utility scores among 5-year survivors (Auckland), compared with the general population, were greatest in the youngest age group (<55 years; **Supplemental Table C-10**). By contrast, the sex differences in EQ5D utility scores between stroke survivors (Oxford) and the general populations appeared to greater among those aged ≥65 years (**Supplemental Table C-9a** and **C-9b**) than those aged <65 years.

5.6 **Discussion**

Women, in unadjusted analyses, had poorer HRQoL at 1 and 5 years after stroke than men across studies. Although the effect estimates varied by outcome measures (i.e. EQ5D, SF36 and AQoL), the direction of the association between sex and HRQoL was relatively consistent between studies, even in those with mapped HRQoL scores. We have examined the contributing factors to the sex differences in HRQoL using the pooled individual long-term outcome data from high-quality population-based studies, overcoming several current caveats of existing research.

The greatest contributors to the worse HRQoL in women were advanced age, pre-stroke functional limitations and stroke severity, but not clinical care. The presence of long-term post-stroke mood disorders also accounted for some of the sex difference in HRQoL. These same factors also accounted for women's worse survival, functional

outcomes and participation restriction in the long term following stroke.[265] The contributing factors could form the basis of interventions to reduce the differences in these outcomes between men and women after stroke.

In pooled analyses, the aforementioned covariates accounted for much, but not all, of the sex differences in long-term HRQoL after stroke (i.e. explained 54% of the pooled MD at 1 year). In study-specific analyses, there was some evidence that women still had worse HRQoL following stroke than men based on the fully-adjusted models although these differences were clinically relevant in fewer studies (1/3 studies at 1 year and 2/3 studies at 5 years).

The important role of age in the association between sex and HRQoL after stroke can be explained by the complexity of aging and comorbidities.[242] The multimorbidity in the elderly should be integrated into management and post-stroke rehabilitation strategies to improve HRQoL in the long term after stroke.[279] More effective primary prevention strategies (e.g. promotion of healthy aging), designed for different levels of cardiovascular diseases and stroke risks[280] should be a priority to improve health for the elderly, many of whom are women.[281]

Another main determinant of poorer long-term HRQoL in women survivors was the presence of functional limitations before stroke. The poorer pre-stroke function in women reflects correlations between sex and age,[236] again highlighting the importance of improving health for older people from both primary and secondary care.

Compared to men, women appeared to present with more severe strokes,[265] which is associated with poor HRQoL after stroke. An implication of this finding is that management of modifiable factors of stroke severity such as hypertension,[244] cardiovascular diseases,[245] and cardioembolic strokes[282] could help mitigate poorer outcomes after stroke in women.

The presence of post-stroke mood disorder (e.g. anxiety, depression) was a contributing factor to the sex differences in HRQoL for the Melbourne study, but not the Auckland study. These inconsistent findings may be due to the variation in assessment scale between studies including the Irritability, Depression and Anxiety (IDA)[190] Scale (Melbourne) and the sub-score of depression the 28-item General Health Questionnaire[192] (GHQ-28; Auckland). This is problematic because the IDA may be more sensitive than the GHQ for detecting depression.[283] It is evident that post-stroke depression (PSD) is more common in women than in men,[168] and the inadequate diagnosis and treatment of PSD may lead to their poorer HRQoL. Acknowledging the complexity in the diagnosis of PSD, including the overlapping symptoms of stroke and depression (especially in the elderly),[284] investigators indicated that only one-fifth of people with PSD were taking antidepressant medications.[191] Also, one-third of patients using antidepressants still reported depressive symptoms,[285] suggesting an insufficient response to treatment. Sex differences in response to PSD treatment and its association with HRQoL are unknown, requiring future research. Better detection and appropriate treatment of PSD should improve the HRQoL for both men and women after stroke. PSD could be prevented by targeting predictive risk factors for PSD such as age, sex, social isolation, stroke severity, mental history, poor functional outcome, and participation

restriction.[284,286] Social and family participation[286] in the prevention of PSD in the elderly, many of whom are women, may provide opportunities to unravel the sex differences in HRQoL after stroke.

In subdomain analyses, the impacts of stroke on the HRQoL of 1- and 5-year survivors were greater in women compared to men in most dimensions of physical and mental health which were mainly explained by pre-stroke factors and post-stroke mood disorders. A potential limitation of these analyses is that the available instruments (EQ5D, AQoL, or SF36) are generic scales. In the few studies of sex differences in HRQoL using stroke-specific instruments (e.g. the Stroke Specific Quality of Life Scale, Stroke Impact Scale), women appeared to have poorer HRQoL in some other domains (i.e., vision, language, thinking, energy, and memory) but sex differences still exist after adjustment for the confounding factors.[104,287] The residual differences between men and women, as mentioned earlier in this paper, may be further accounted for by unmeasured or poorly measured factors such as psychosocial or mood disorders, requiring further research.

Authors of previous research in stroke have usually reported a statistically significant difference in utility scores between the sexes but less often considered the clinical relevance of these findings across HRQoL instruments.[276-278] Women in the general population may also have poorer HRQoL compared to their male counterparts, particularly in older age groups.[271,276] However, there is a lack of studies investigating the sex difference in comparison with the general population. In our analyses in comparison with population reference scores by region, the statistically significant differences in utility scores between women and men among stroke and general

populations existed in some age groups but varied among studies and HRQoL instruments. We found significant sex differences in HRQoL after stroke assessed by SF6D (Auckland, NZ) or AQoL (Melbourne, Australia) utility scores, after accounting for sex differences in the population, among younger (<65 years) than older groups (≥ 65 years); and vice versa for the EQ5D instrument (Oxford, UK). Interestingly, the findings of greater sex differences in HRQoL loss caused by stroke among those aged ≥ 65 years were consistent with the similar analyses using the EQ5D data from the Australian Stroke Clinical Registry – a national stroke registry (**Chapter 10** of the thesis). It is possibly related to the scale discrepancy whereby some social aspects of SF36 or AQoL, e.g. social functioning or family role (**Supplemental Table C-11**; source: Hawthorne et al., 2005)[288] that may contribute to the greater health loss for younger women than younger men were not captured by the EQ5D instrument. Another possibility is the impact of variability in self-reported HRQoL due to different demographic, economic, cultural and social factors across populations. A previous examination of national culture and HRQoL evaluations showed that Australia is closer to NZ on masculinity index (gender role), uncertainty avoidance (to prevent anxiety/depression) and long-term orientation (coping skills or adaptation) than it is to UK.[289] Future studies of sex differences in HRQoL should consider the comparison with population norms, contributions of cultural factors, and the clinically significant difference.

We found that stroke caused a substantial HRQoL loss for both men and women in the long term following stroke, consistent with previous research by Cadilhac and colleagues.[21] Our study showed that a considerable proportion of people with strokes were not treated with evidence-based therapies such as intravenous thrombolysis for

ischaemic stroke. The finding suggests that when stroke happens, ensuring that everyone has access to evidence-based processes of care in the hospital that are associated with better HRQoL (i.e. stroke unit care, thrombolytic therapy, antihypertensive agents, and care plan at discharge)[60] should be a priority.

Our research has several strengths. We used individual long-term outcome data from high-quality population-based studies representative of different countries.[30] To our knowledge, this is the largest study every performed to comprehensively examine the contributing factors to the sex difference rather than using a step-wise approach overcoming the limitations of previous studies. Our study assessed a broad range of potential factors that contribute to the sex difference in HRQoL. Two-stage meta-analysis was used to compare the sex differences between the populations to overcome the variability in HRQoL measures and covariates. We also compared the net mean difference in HRQoL utility scores between people with stroke and the general population to see how stroke impacts on men and women's health. Our analyses using mapped scores served as a surrogate for the absence of HRQoL assessment in many 'ideal' population-based studies.

We have acknowledged a number of limitations in this study. The HRQoL assessment was only available in 3 studies at each time point (1 and 5 years after stroke). The number of studies forming our pooled estimates, even among those with mapped utility scores (n=8 studies), was less than required (≥10) for the exploration of heterogeneity between studies using meta-regression.[231] The included cohorts were mostly conducted in high-income countries so the results might not be generalisable to low- and middle-income countries (LMICs). Some previous studies from LMICs

presented a lower HRQoL among women than men in the long term after stroke (e.g. China 2 years;[114] Malawi 1 year[290]) but they were not based in the population. Although we identified some other eligible studies that are ideal for examining the sex difference through systematic search during this period, the investigators failed to either report sex-specific results or have the HRQoL assessment performed.[265] We advocate the inclusion of longer-term outcomes in such studies in future research to assess sex differences in HRQoL, particularly in LMICs.

Some potential confounding factors were not measured in all studies including stroke care and post-stroke factors. Our analyses of available data on treatment and management of stroke suggested that this did not affect the sex difference in HRQoL after stroke, but the studies with more comprehensive data (Melbourne, Perth, and Auckland) were conducted a long time ago. Further work should confirm whether the difference in the contemporary processes of hospital care could have an impact on sex differences in HRQoL and associated factors. Among studies with measured HRQoL, only two had long-term assessments of mood disorders. Depression accounted for 22-41% of worse HRQoL in women up to 5 years after stroke for the Melbourne study (assessed by the IDA) but not for the Auckland study (the 28-item General Health Questionnaire). The variability in measures of outcomes and covariates between studies from different populations may bias the adjusted estimates in our analyses. Another limitation is the relatively high proportion of loss to follow-up among studies (Perth: 1 year; Auckland: 5 years). Sensitivity analyses using multiple imputation and inverse probability weighting may somewhat account for the missing data but we could not remove the possibility of selection bias.

Conclusion

Women generally have poorer long-term HRQoL after stroke in most dimensions of physical and mental health. The sex differences were mostly explained by women's advanced age, pre-stroke function, and stroke severity with some evidence that PSD was also important. Targeting 'potentially modifiable' factors including stroke severity and mood disorders will provide more opportunities to reduce the sex differences in stroke outcomes. Better prevention and management of PSD, including early detection and appropriate treatment, are of importance to improve the HRQoL of stroke survivors. Those men and women with stroke, compared to the general population, have reasonably similar HRQoL loss. Therefore, strategies should be focused on all stroke survivors to improve HRQoL following stroke.

Table 5-1. Details of included cohorts, baseline with first-ever stroke cases

Study	Study year	Baseline, n	Instrument	1-year follow-up		5-year follow-up	
				Survivor, n	Assessed, n	Survivor, n	Assessed, n
Oxford, United Kingdom	2002-2013	1374†	EQ5D	988	712	403	269
			EQ5D*		910*		385*
Joinville, Brazil	2009-2014	2248	EQ5D*	1869	1708*	598	423*
Melbourne, Australia	1996-1999	1248‡	AQoL	806	465	553	450
Arcadia, Greece	1993-1995	555	EQ5D*	342	328*	-	-
Perth, Australia	2000-2001	183	SF36	120	33	-	-
			EQ5D*		36*	-	-
Orebro, Sweden	1999-2000	377‡	EQ5D*	253	253*	-	-
Martinique, French West Indies	1998-1999	580	EQ5D*	391	391*	265	265*
Porto, Portugal§	1998-2000	688	EQ5D*	484	484*	281	259*
Auckland, New Zealand	2002-2003	1423	SF36	-	-	881	338
			EQ5D*		-		745
Tartu, Estonia§	2002-2003	433‡	EQ5D*	245	194*	161	131*
Total cases		**9,109**‖		**1,914** or **5,498***	**1,210** or **4,303***	**1,837** or **3,142***	**1,057** or **2,208***

AQoL=Assessment of Quality of Life;[195] EQ5D=European Quality of Life–5 Dimensions;[194] SF36=Short form–36 questions[266]

* denotes EQ5D utility score mapped from the modified Rankin Scale

† Follow-up data to 5 years after stroke were available only among cases with year of stroke until 2008 (’02-’08) with 760 cases at baseline

‡ Not including those with a subarachnoid haemorrhagic stroke at baseline

§ Follow-up data that were available only at 4 years (for Tartu) or 7 years (for Porto) were analysed as an alternative to 5-year outcome

‖ There were 7,295 cases at baseline among studies have 5-year data

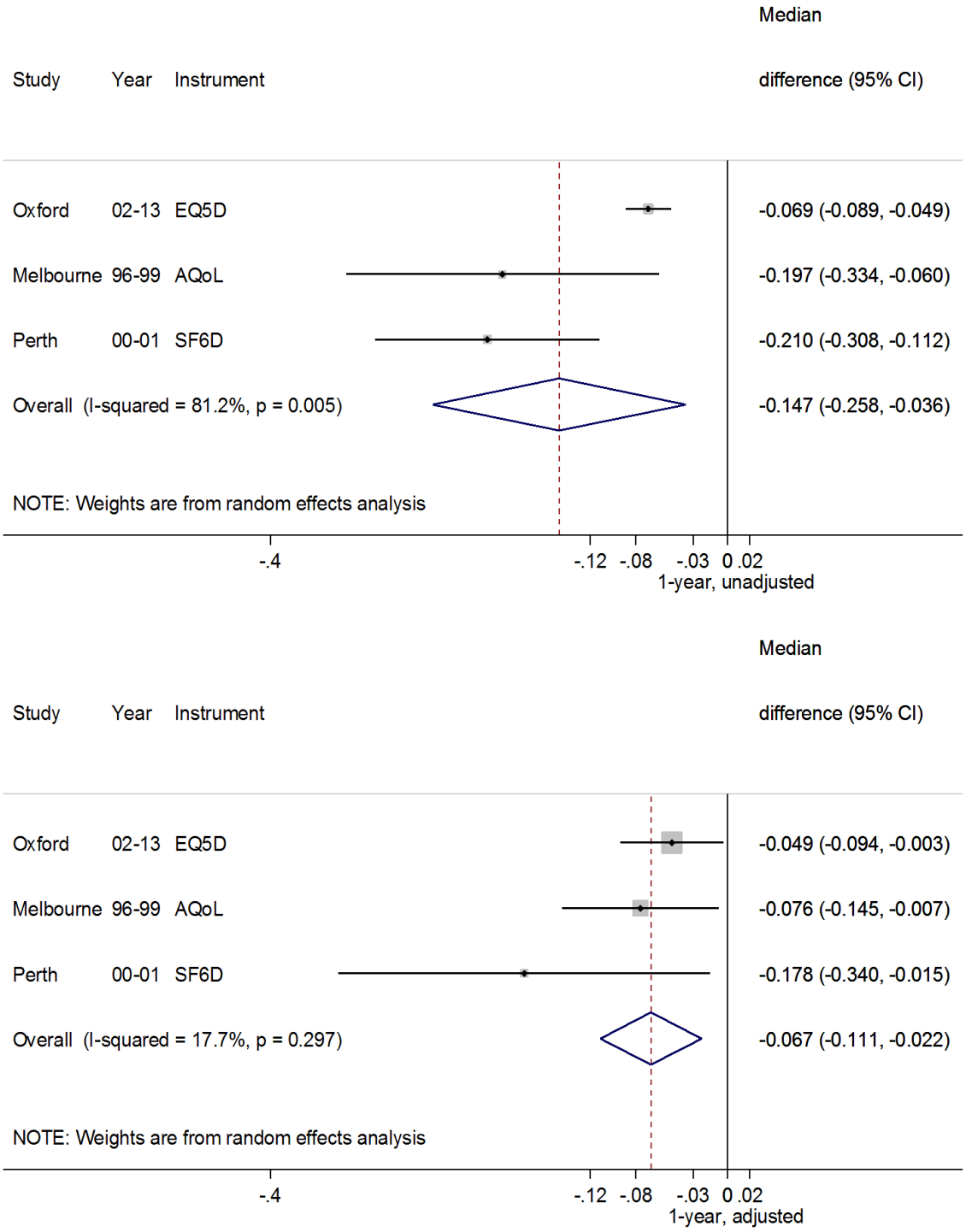


Figure 5-1. Median difference in utility scores for women compared to men at 1 year after stroke in unadjusted (top panel) and adjusted (bottom panel) models from three studies. The differences at 0.06 for AQoL, 0.12 for EQ5D, and 0.08 for SF6D were considered as clinically relevant (see Methods).

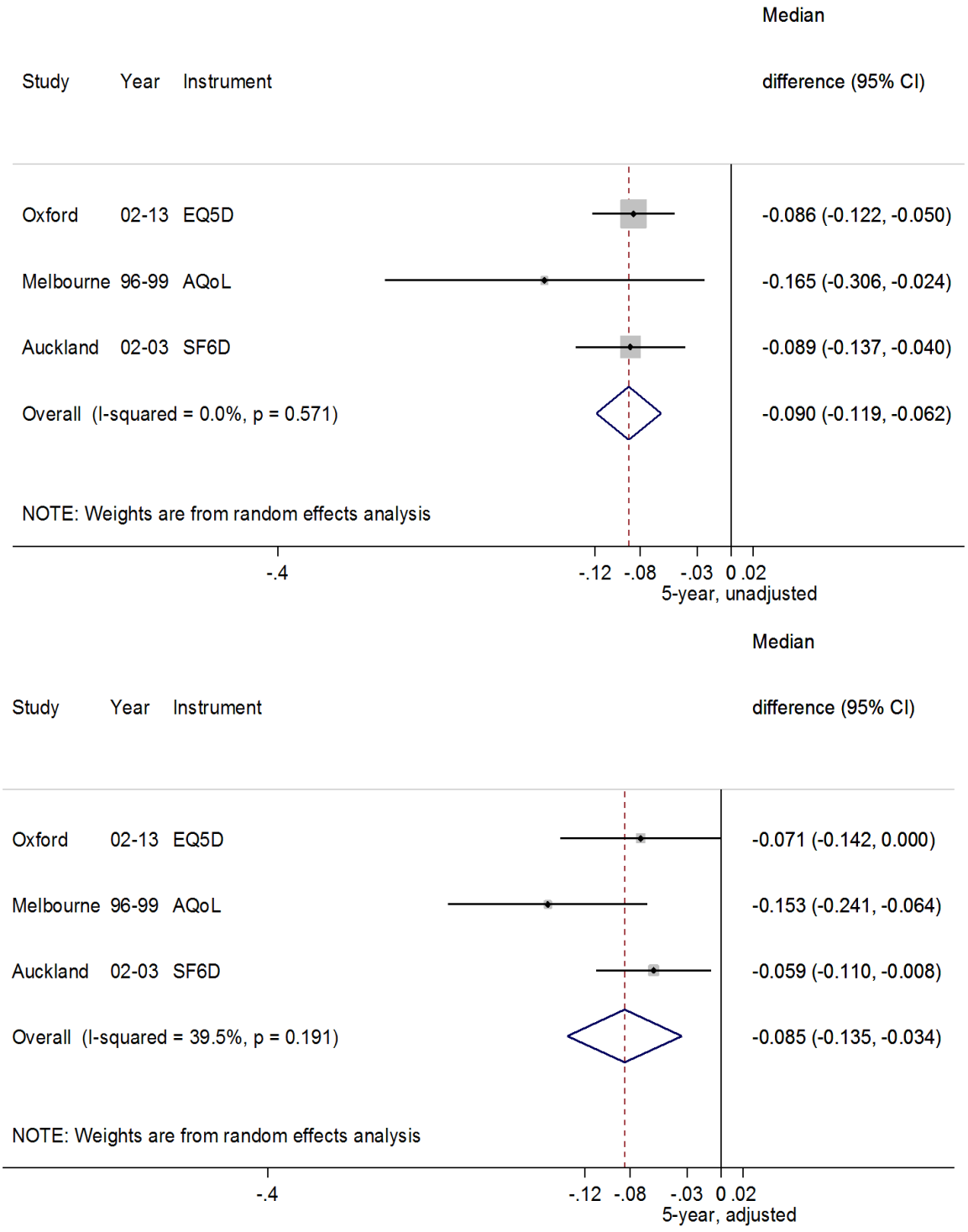


Figure 5-2 Median difference in HRQoL utility scores for women compared to men at 5 years after stroke in unadjusted (top panel) and adjusted (bottom panel) models from three studies. The differences at 0.06 for AQoL, 0.12 for EQ5D, and 0.08 for SF6D were considered as clinically relevant (see Methods).

Table 5-2. Factors contributing to the median difference (MD) in utility scores at 1 year after stroke for women compared to men

	Oxford (EQ5D; n=700)				Melbourne (AQoL; n=385)				Perth (SF36; n=31)			
	MD	95%	CI	Δ*	MD	95%	CI	Δ*	MD	95%	CI	Δ*
Unadjusted	-0.069	-0.089	-0.049		-0.197	-0.334	-0.060		-0.210	-0.308	-0.112	
Adjusted for												
Age	-0.060†	-0.096	-0.025	13%	-0.162†	-0.263	-0.061	18%	-0.205†‡	-0.341	-0.068	2%
NIHSS	-0.067†‡	-0.107	-0.028	2%	-0.173†	-0.262	-0.083	12%	-0.193†‡	-0.312	-0.074	8%
Pre-stroke Rankin	-0.061†	-0.087	-0.034	12%	----				-0.204†‡	-0.380	-0.028	3%
Pre-stroke Barthel	---				-0.187 †‡	-0.295	-0.080	5%	----			
Marital status	-0.052	-0.912	-0.013	25%	----				-0.179	-0.301	-0.058	15%
Pre-stroke dementia	---				-0.173	-0.278	-0.068	12%	----			
1-y mood disorder (IDA)	---				-0.116†	-0.206	-0.026	41%	----			
1-y Barthel	---				-0.135	-0.211	-0.058	31%	----			
1-y Rankin	-0.014	-0.015	0.012	80%	----				-0.072	-0.180	0.036	66%
Full model	-0.049	-0.093	-0.004	29%	-0.076	-0.145	-0.007	61%	-0.178	-0.340	-0.015	15%
Further adjustment§	-0.018	-0.058	0.022	73%	-0.056	-0.113	0.001	72%	-0.064	-0.017	0.041	70%

AQoL=Assessment of Quality of Life;[195] EQ5D=European Quality of Life–5 Dimensions;[194] SF36=Short form–36 questions[266]
NIHSS=National Institutes of Health Stroke Scale; IDA= the Irritability, Depression and Anxiety Scale (continuous score); 1-y=1-year
* % change of coefficient of sex difference between unadjusted and adjusted models was calculated by the formula (unadjusted β – adjusted β)/ unadjusted β *100
† denotes covariates which remained in the full models; ‡ not meeting criteria of being a confounder but retaining in the fully adjusted multivariable model; § Full model with further adjustment for functional outcome at 1 year (modified Rankin scale or Barthel Index)

Table 5-3. Factors contributing to the median difference (MD) in utility scores at 5 years after stroke for women compared to me

	Oxford (EQ5D; n=263)				Melbourne (AQoL; n=363)				Auckland (SF6D; n=301)			
	MD	95%	CI	Δ*	MD	95%	CI	Δ*	MD	95%	CI	Δ*
Unadjusted	-0.086	-0.122	-0.050		-0.165	-0.306	-0.024		-0.089	-0.137	-0.040	
Adjusted for												
Age	-0.068†	-0.126	-0.010	21%	-0.207†	-0.327	-0.088	-25%	-0.069†	-0.120	-0.019	22%
NIHSS	-0.091†‡	-0.146	-0.035	-6%	-0.207†	-0.317	-0.097	-25%	---			
GCS	---				---				-0.099†	-0.149	-0.049	-11%
Pre-stroke Rankin	-0.048†	-0.129	0.033	44%	---				---			
Pre-stroke Barthel	---				-0.163†‡	-0.307	-0.019	1%	---			
Pre-stroke dependency	---				---				-0.073†	-0.122	0.024	18%
Marital status	-0.036	-0.097	0.025	58%	---				-0.084	-0.136	-0.032	6%
Pre-stroke dementia	---				-0.149	-0.292	-0.006	10%	---			
5-y mood disorder (IDA)†	---				-0.129	-0.276	0.018	22%	---			
5-y antidepressant medications	---				-0.187	-0.272	-0.101	-13%	---			
5-y Rankin	0	-0.057	0.057	100%	---				-0.039	-0.069	-0.010	56%
5-y Barthel	---				-0.075	-0.151	-0.0003	54%	---			
Final model	-0.071	-0.142	0.000	17%	-0.153	-0.241	-0.064	7%	-0.059	-0.110	-0.009	34%
Further adjustment§	-0.012	-0.068	0.043	86%	-0.040	-0.096	0.016	76%	-0.033	-0.066	-0.0003	63%

AQoL=Assessment of Quality of Life;[195] EQ5D=European Quality of Life–5 Dimensions;[194] SF36=Short form–36 questions[266]
GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; IDA= the Irritability, Depression and Anxiety Scale (continuous score); 5-y=5-year
* % change of coefficient of sex difference between unadjusted and adjusted models was calculated by the formula (unadjusted β – adjusted β)/ unadjusted β *100; † denotes covariates which remained in the full models; ‡ not meeting criteria of being a confounder but remaining in the fully adjusted multivariable model; § Full model and further adjustment for functional outcome at 5 years (modified Rankin scale or Bathel Index)

5.7 Supplemental Methods

Statistical analysis

Because covariates were not measured uniformly between studies, we could not harmonise and adjust for the same set of covariates. Hence, a two-stage analysis method[204] for the analysis of pooled data was used. In the first stage, study-specific models for the sex difference in health-related quality of life (HRQoL) were built. Within each study, the role of the covariates as confounders of the association between sex and HRQoL outcome were assessed using purposeful model building techniques.[207] The following rules were applied: 1) the covariate was associated with HRQoL ($p<0.1$); 2) the covariate was associated with sex ($p<0.1$), and 3) the inclusion of the covariate in the model with only sex changed the magnitude of the sex coefficient at least 10%.[207]

Age, stroke severity, and pre-stroke dependency that are common predictors of HRQoL and associated with sex,[23,24] where possible, were forced into the final multivariable models accounting for all significant confounding factors. Given a high correlation between HRQoL and functional outcome,[273] we did not include long-term functional outcome in the final models to avoid over-adjustment bias. Further adjustment for this factor was separately reported.

In the second stage of the analysis, the effect estimates from unadjusted and multivariable models were combined to create pooled estimates in separate random-effects meta-analyses. Statistical heterogeneity between studies was evaluated using I^2 statistics. The potential sources of heterogeneity were assessed among variables of interest using meta-regression.[231] Variables of interest in meta-regression included in the supplement xx.

Potential sources of heterogeneity

Potential sources of heterogeneity were assessed among variables of study-level characteristics (e.g. geographic region, income group) using meta-regression. In these analyses, we calculated separate pooled effect estimates of sex differences in long-term HRQoL utility scores mapped from the mRS (8 studies at 1 year; 6 studies at 5 years) for models both unadjusted and adjusted for actual confounding factors, when appropriate. Meta-regression of continuous variables (n=3 variables) of interest included: proportion of women, proportion of hospital admission, mid-point of study year (e.g. in the Oxford study, year of stroke ranged from 2002 to 2013, and the mid-point was 2008).

There were three covariates measured consistently in all studies: year of stroke occurrence (ranged from 1993 to 2014), age at stroke onset and stroke type. To further test the robustness of our findings, we used a single-stage meta-analysis pooling all IPD datasets[210] to examine whether these factors modified the sex-effect HRQoL after stroke. We chose $p \leq 0.10$ as the cut-off for statistical significance of the interaction (sex × covariate product term) because this value is commonly accepted in the literature for detecting interactions.[291]

Missing data and sensitivity analyses

We undertook a wide range of sensitivity analyses to assess other potential bias. For studies with >20% missing data of long-term functional outcomes, participation or covariates, multiple imputation using chained equations (n=50 imputations) combined with Inverse-Probability Weighting[241] was performed and compared with results from complete-case analyses. These sensitivity analyse were based on the assumption that the data were missing at random. The missing values of outcomes and all covariates, where necessary, such as severity and co-morbidities were imputed based on all remaining completed variables in the dataset. We then examined whether the exclusion of those with a high rate of missing data on outcomes and confounding factors influenced our pooled results by comparing the sex differences in HRQoL for complete-case analysis and imputed analysis with unadjusted and fully-adjusted models.

Chapter 6: Sex differences in severity of stroke in the INternational STRoke oUtComes sTudy (INSTRUCT): a meta-analysis of individual participant data

6.1 Preface

At the time of submission of this thesis, the contents of this chapter have been under review following request for revisions from the *Journal of American Heart Association.*

Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, Otahal P, Rothwell P, Bejot Y, Cabral NL, Appelros P, Kõrv J, Vibo R, Minelli C, Gall SL. Sex differences in severity of stroke in the INternational STRoke oUtComes sTudy (INSTRUCT): a meta-analysis of individual participant data.

6.2 Abstract

Background: Women have worse outcomes after stroke than men, and this may be partly explained by stroke severity. We examined factors contributing to sex differences in severity of acute stroke assessed by the National Institutes of Health Stroke Scale (NIHSS).

Methods: We pooled individual participant data with NIHSS assessment (n=6,343) from eight population-based stroke incidence studies (1996-2014). Information on socio-demographics, stroke-related clinical factors, comorbidities and pre-stroke

function were obtained. Within each study, log-binominal modeling was used to estimate the female:male relative risk (RR) of more severe stroke (NIHSS>7) stratified by stroke type (ischaemic stroke—IS and intracerebral haemorrhage—ICH). Study-specific unadjusted and adjusted RRs, controlling for confounding variables, were pooled using random-effects meta-analysis.

Results: NIHSS data were recorded in 5326 (96%) of 5570 cases with IS and 773 (90%) of 855 participants with ICH. The pooled unadjusted female:male RR for severe IS was 1.35 (95% CI 1.24–1.46). The sex difference in severity was attenuated after adjustment for age, pre-stroke dependency, and atrial fibrillation but remained statistically significant (pooled $RR_{adjusted}$ 1.15, 95% CI 1.05–1.27). There was no sex difference in severity for ICH (RR_{crude} 1.08, 95% CI 0.97–1.21; $RR_{adjusted}$ 1.08, 95% CI 0.96–1.20).

Conclusion: Although women presented with more severe IS than men, much although not all of the difference was explained by pre-stroke factors. Sex differences could potentially be ameliorated by strategies to improve pre-stroke health in the elderly, the majority of whom are women. Further research on the potential biological origin of sex differences in stroke severity may also be warranted.

6.3 Introduction

Women are less likely to survive following stroke because of a higher case fatality rate in the acute phase, but long-term sex differences in mortality persist up to 5 years after stroke.[236] Women also often have poorer functional outcome, increased participation restriction, and lower health-related quality of life after stroke than

men.[236,265] One explanation for these sex differences in outcome is that women have more severe strokes than men.[84,236] While several studies have reported on sex differences in the severity of stroke, most often these studies use severity as a covariate rather than as a primary outcome. [110,229] Another challenge is that the measurement of severity can differ between studies.[208,292,293] Thus the importance of and factors associated with sex differences in stroke severity, remain uncertain.[84] Although there are reports on factors that contribute to severity of stroke (e.g. hypertension,[244] cardiovascular diseases,[245] dementia,[294] embolic stroke mechanism[295]), the relative importance of these factors to differences in severity between women and men has not been investigated thoroughly.

Among the few studies designed to examine the aetiology of sex differences in stroke severity,[94,296] there are important differences in the data sources, methods of analysis, and adjustment for confounding factors. Renoux et al[296] reported a 49% (unadjusted OR 1.49, 95% CI 1.23–1.80) increased odds of having a severe stroke (NIHSS ≥5) for women compared to men, which was partly explained by age and pre-stroke modified Rankin Scale—mRS (adjusted OR 1.19, 95% CI 0.94–1.52 following adjustment for these two variables). In contrast, Gall and colleagues reported a 23% (unadjusted RR 1.23, 95% CI 1.05–1.45) greater risk of severe stroke (NIHSS>7) in women; but the difference was almost completely explained by women's older age, presence of dementia, atrial fibrillation, and pre-stroke Barthel Index (adjusted RR 1.05 95% CI 0.91-1.22).[94] Other than age, pre-stroke functional limitations, and comorbidities, there has been limited consideration on the influence of other potential confounding factors such as pre-stroke medication[297], delay in presenting to the hospital,[298] and

mechanism of ischaemic stroke (i.e. cardioembolic strokes)[282] on the sex difference in severity.

Examination of a wider range of potential contributors to any observed sex difference in stroke severity is important to help address the gaps in our understanding of factors affecting sex-specific difference in stroke outcomes. Using information from an individual participant data (IPD) meta-analysis we aimed to (1) quantify the sex difference in stroke severity assessed by initial the National Institutes of Health Stroke Scale (NIHSS) score among patients with first-ever acute stroke (both ischaemic and haemorrhagic), and (2) investigate the factors (i.e. sociodemographics, pre-stroke health, comorbidities and clinical factors) that contribute to any observed difference.

6.4 **Method**

The INternational STRoke oUtComes sTudy (INSTRUCT) — an IPD meta-analysis of long-term outcomes after stroke — is a collaboration of investigators from 13 'gold standard' population-based stroke incidence studies (limited to first-ever acute strokes) from Australasia, Europe, South America and the Caribbean. The INSTRUCT study was registered in PROSPERO (CRD42016036723)[237] and performed according to PRISMA-IPD guidelines.[203] Further details regarding the INSTRUCT study are provided in **Chapter 2**.

6.4.1 Outcome measurement

Of the 13 studies forming the INSTRUCT, eight studies had data on National Institutes of Health Stroke Scale (NIHSS) scores recorded at the acute stage and so were included in this analysis. The NIHSS assessment was recorded directly in seven studies and responses were mapped from Scandinavian Stroke Scale (SSS) data available in one other study (Tartu) using the formula: $SSS = 50 - 2 \times NIHSS$.[189]

6.4.2 Predictors of outcome (covariates)

We obtained data on a range of covariates in each cohort that might explain differences in stroke severity between men and women. These factors included: socio-demographics, pre-stroke health (functional dependence, co-morbidities, health behaviours, pre-stroke medications), stroke type; acute management (hospital admission, time delay to hospital presentation), and the year of stroke occurrence (1996-2014). Details regarding how these data were collected and the definitions used for each variable in each specific study are provided in **Chapter 2**: section **2.5**. Available sociodemographic data included *race/ethnicity* (2 studies), *marital status* (4 studies), *education* (4 studies), and *socioeconomic status* (3 studies). Data on pre-stroke health status included *dependence before stroke* (4 studies, mRS >2; 3 studies, Barthel Index ≤20; 4 studies, institutional residence); *co-morbidities/medical history* (all studies— atrial fibrillation, hypertension, ischaemic heart disease, transient ischaemic attack; 5 studies, peripheral vascular disease; 4 studies, diabetes; 3 studies, dementia); *medications before stroke* (4 studies, antihypertensives; 4 studies, antiplatelets; 1 study, anticoagulants); *body mass index* (5 studies), and *health behaviours* (7 studies, smoking status; 6 studies, alcohol use status). Type of stroke

was categorised into 4 groups: ischaemic stroke (IS), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) and undetermined stroke. Ischaemic stroke subtypes, available in 4 studies, were categorised by TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification[299] including large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and other determined aetiology.

6.4.3 Statistical analysis

All analyses were conducted in Stata 12.1. A two-tailed P-value ≤0.05 was considered statistically significant.

Study-specific analyses of the characteristics of participants (e.g. mean age, % of pre-stroke functional limitation) were compared between men and women and then pooled using random-effects meta-analysis. We only undertook analyses for IS and ICH because NIHSS was not routinely collected for SAH and undetermined stroke. Stroke severity was dichotomised into severe (NIHSS>7) or not-severe (NIHSS ≤7).[94] Given the uncertainty over the particular cut-point to use to define a severe stroke, we also undertook a sensitivity analysis by analysing NIHSS as a continuous outcome. Where necessary, transformations of NIHSS data were performed to remove skewness.

Since covariates were not measured uniformly between studies, we could not harmonise the data in order to conduct a multivariable analysis of the pooled IPD. We, therefore, used the two-stage method of analysis proposed for IPD meta-analyses.[204]

The first stage involved building study-specific unadjusted and adjusted log-binomial regression models to estimate the relative risk of severe stroke (NIHSS>7 vs ≤7) for women compared to men. Within each study, we assessed the confounding role[207] of covariates in the association between sex and severity, separately for IS and ICH. Variables were entered into the multivariable models if they met the following 4 criteria (missing <20% of cases, associated with sex, associated with stroke severity, and the inclusion of the covariate changed the magnitude of the sex coefficient by ≥10%).[24] Adjustment was first done for age and then for all identified confounding factors but with age forced into a final fully-adjusted model. Within each study, statistical interactions were assessed by a test of statistical significance of a sex × covariate product term. For the second stage of the analysis, both unadjusted and adjusted study-specific estimates were pooled in separate random-effects meta-analyses. Heterogeneity was evaluated using Q statistics and I^2 statistics. Meta-regression was used to identify the sources of statistically significant heterogeneity among study-level characteristics including geographic regions and proportion of women.

We also reported the subgroup analyses of the difference in severity of IS by TOAST subtype. Sensitivity analyses using NIHSS as a continuous variable were performed to compare with the main results of dichotomous analyses.

Two covariates were measured consistently in all studies: year of stroke occurrence and age. To further test the robustness of our findings, we used a single-stage meta-analysis pooling all IPD datasets[210] to examine whether these factors modified the relationship between sex and stroke severity.

6.5 **Results**

Sex difference in patient characteristics

Data on initial NIHSS recorded after acute stroke onset were available among 5326/5570 (95.6%) IS and 773/855 (92.6%) ICH participants of the eight studies (**Appendix D**: **Supplemental Tables D-1a** and **D−1b**). Among those with IS, compared to men, women were on average 4.5 years (95% CI 3.8-5.3) older (statistically significant difference in 6/8 studies; **Table 6-1**) and were less likely to be living with a spouse (summary estimate 39.4% vs 71.2%, p<0.001; significant difference in 3/4 studies). Women also had higher prevalence of functional limitation (mRS>2 or Barthel≤20) before stroke (summary estimate 22.6% vs 14.0%, p<0.001; significant difference in 2/5 studies) and institutional residence than men (summary estimate 12.0% vs 4.6%, p<0.001; significant difference in 3/4 studies). In IS, more women were prescribed anti-hypertensive agents (3/5 studies) before stroke than men. Men with IS were more often ever-smokers (significant difference in 7/7 studies) and consumers of alcohol (significant difference in 4/6 studies). Among ICH participants, women were on average 4.7 years (95% CI 2.6-6.7) older than men (significant difference in only 3/8 studies), and there was few difference in other baseline characteristics between women and men (**Supplemental Tables D-1a** and **D−1b**).

Distribution of the NIHSS by sex among those with either IS or ICH was illustrated in **Figure D-1** (n=6,099; eight studies).

Analyses of initial NIHSS scores among eight studies included 5200/5326 participants with IS (**Table 6-2**; 2% of cases were excluded due to missing data on

covariates). In unadjusted analyses, women with IS were 35% (pooled RR 1.35, 95% CI 1.24–1.46) more likely to suffer more severe strokes than men; study-specific crude RRs varied from 1.20 (Perth) to 1.71 (Mãtao; **Figure 6-2**, top). We found no statistical evidence of heterogeneity in unadjusted RR estimates (I^2=0%; Q=4.4, p=0.732) across the studies. In multivariable analysis, adjustment for age alone reduced the sex difference in severity by 36% (pooled $RR_{age\text{-}adjusted}$ 1.21, 95% CI 1.11–1.31) without a statistical heterogeneity (I^2=0%; Q=4.9, p=0.670). After accounting for other confounding variables (e.g., AF, pre-stroke dependency), the pooled estimate was substantially attenuated but remained statistically significant (pooled $RR_{fully\text{-}adjusted}$ 1.15, 95% CI 1.05–1.27). Although study-specific adjusted RRs of the association between sex and severity of IS varied from 0.97 (Dijon) to 1.72 (Mãtao) there was no statistically significant heterogeneity between studies (I^2=19%; Q=8.6, p=0.280; **Figure 6-2**, bottom). Factors that met all the criteria for being a confounder were inconsistent between studies (**Table 6-2**). Among IS, these confounding factors were age (6/8 studies, pre-stroke dependency (5/6 studies), atrial fibrillation (2/8 studies), history of dementia (1/3 studies) and smoking (1/7 studies). None of these factors modified the effect of sex on stroke severity (i.e., all sex × covariate interactions were non-significant). There was also no evidence that IS subtype (TOAST; **Supplemental Table D-2**), or any of the other covariates (e.g., socioeconomic position, education, pre-stroke medications, alcohol use, and other comorbidities such as diabetes and hypertension) contributed to the sex difference in NIHSS (**Supplemental Table D-3**).

Analyses of 855/773 participants with ICH (**Table 6-2**; 10% of cases were excluded due to missing data on confounding factors) found no sex difference in the severity of

stroke (pooled $RR_{unadjusted}$ 1.08, 95% CI 0.97–1.21; **Figure 6-3**, top) without a statistical heterogeneity (I^2=0%; Q=2.1, p=0.957). There was no effect of adjusting for age with the age-adjusted pooled RR being 1.08, 95% CI 0.96–1.20 (**Figure 6-3**, bottom; I^2=0%; Q=1.4, p=0.985) or any other covariates.

Meta-regression did not identify any sources of the heterogeneity between studies. Neither study-level factors including geographic region, the availability of pre-stroke function (**Supplemental Table D-4a**) nor proportion of women modified the sex differences in both unadjusted (IS: $P_{meta\text{-}regression}$=0.559; ICH: $P_{meta\text{-}regression}$=0.726) and adjusted analyses ($P_{meta\text{-}regression}$=0.403; ICH: $P_{meta\text{-}regression}$=0.723). Removing two studies without data on pre-stroke function (Supplemental Figures 2-3) did not greatly influence the pooled estimates in both unadjusted and adjusted analyses (IS: pooled $RR_{unadjusted}$ 1.30, 95% CI 1.18-1.44; $RR_{adjusted}$ 1.10, 95% CI 0.98-1.23; ICH: $RR_{unadjusted}$ 1.12, 95% CI 0.97-1.30; $RR_{adjusted}$ 1.12, 95% CI 0.97-1.30). Sensitivity analyses using NIHSS as a continuous variable showed consistent results to dichotomous analyses (**Supplemental Table D-5**).

In participant-level analyses of the single pooled IPD dataset, the effect of age as a confounding factor was similar (IS: pooled $RR_{unadjusted}$ 1.34, 95% CI 1.22-1.49; $RR_{age\text{-}adjusted}$ 1.21, 95% CI 1.10-1.34; ICH: pooled $RR_{unadjusted}$ 1.08, 95% CI 0.90-1.29; $RR_{age\text{-}adjusted}$ 1.08, 95% CI 0.90-1.29) to the one using the aforementioned two-stage approach. The magnitude of the sex differences in severity among those with IS and ICH was not modified by age group (**Supplemental Table D-4b**). Neither did the year of stroke occurrence modify the sex differences in stroke severity in both

unadjusted (IS: $P_{interaction}$=0.067; ICH: $P_{interaction}$=0.128) and age-adjusted analyses (IS: $P_{interaction}$=0.264; ICH: $P_{interaction}$=0.281).

6.6 **Discussion**

We found that women with IS faced a 35% greater risk of severe stroke than men, and that much of this difference was explained by women's older age, the presence of functional limitations before stroke and atrial fibrillation. However, adjustment for these factors did not fully explain the sex difference and their effects were often inconsistent between studies. We also found that there was no sex difference in severity of ICH.

Because of the more advanced age at stroke onset in women than men, age was the most important confounding factor of the association between sex and severity of IS, accounting for 36% of the sex difference. Older age may be associated with more severe strokes due to reduced functional capacity of supporting brain cells, i.e. endothelial cells, and astrocytes after neurological insults.[212] The physiological decrease of cerebral blood flow and its regulation that occurs with increasing age[300] potentially influence neuronal damage after stroke in the elderly. As a consequence, impaired brain circulation and subsequent neurological dysfunction might lead to more severe strokes and less recovery in older adults with stroke. A better understanding of the pathophysiology of both stroke and cognitive function in the elderly may have important implications for clinical management and preventative strategies. Strategies such as enhancing geriatric care may help to reduce the poor outcome of chronic diseases[242] including stroke among frail older community-dwelling adults.[301]

Pre-stroke function was an important confounding factor of the sex differences in stroke severity in several (5/6) studies. The association between more severe stroke in women and their poorer functional limitation before stroke has been shown to be correlated with age and several cardiovascular comorbidities (e.g. AF, hypertension, diabetes) at baseline.[227,296] Poor physical function and interrelated conditions such as frailty, which is more common in women,[302] may reflect underlying biologic mechanisms, including chronic inflammation, that play an important role in the pathogenesis of IS and the severity of the brain tissue damage.[303] Better management of comorbid diseases and prevention of frailty in the elderly[220] could help ameliorate the effects of more severe strokes when they occur in women.[94] It is also possible that poor pre-stroke function and the presence of frailty may affect the accurate measurement of items in the NIHSS, as reported by others.[304] Combining clinical, imaging and biomarker data of the severity of stroke may provide a better assessment of severity than a single instrument like the NIHSS.[305]

Atrial fibrillation (AF) contributed to the sex difference in severity of IS although surprisingly this was only important in two out of eight studies (Oxford and Orebro). The inconsistent findings may due to the variations in the data collection and definition of AF between studies (Chapter 2: **Table 2-4**). One reason for more severe strokes in women is that women with AF more often have cardioembolic strokes than men.[222] In addition, previous studies have found that the management of AF, specifically, treatment with anti-coagulants[223] or catheter ablation[224] appears to be suboptimal for women compared to men. It is thus possible that our observed confounding effect of AF on stroke severity could reflect the widespread under-treatment of AF in older patients.[225] However, we cannot confirm this possibility as

treatments for AF were missing from our dataset. This highlights the need for the better detection and treatment of AF in both older men and women prior to stroke occurrence.[306] The data on the presence of AF and management in the incidence studies in the INSTRUCT were mostly self-reported and only included a limited number of studies. This may have contributed to the inconsistent findings. Data linkage may be useful for better examining these associations in men and women but could also suffer from issues related to data quality. Thus, more population-based stroke studies with diagnosed AF and long-term follow-up as well as qualitative research are needed to understand the decision-making for treatment therapies and management of AF, particularly among those with stroke. Recent evidence has shown that 30-day ECG monitoring improved the AF detection and the rate of anticoagulation treatment among those with cryptogenic stroke.[307] Cardiac imaging could be a fertile ground for improvements in diagnose and effective treatment of AF to improve outcomes after stroke.

Age, AF and pre-stroke function combined only accounted for 53% of the sex difference in severity of IS (with RR reduced from 1.35 to 1.15). Other unmeasured or poorly measured confounding factors could explain the remaining difference. However, it is also possible that a true biological or pathophysiological sex difference does exist. Further research is needed to explore potential biological and clinical mechanisms that could lead to a greater stroke severity in women. Potential dimorphic differences between men and women in severity of stroke include biologic (e.g. hormone-dependent) and intrinsic (non-hormonal) factors (e.g. sex chromosomes).[308] Research on biologic mechanisms has established the neuroprotective effect of hormones in women on IS injury during pre-menopause.[308]

Little is known about how the decline of sex steroid hormones in women after menopause and ovariectomy influences the sex differences in post-stroke neurologic deficits. Further examination of the sex differences in neurologic function, specifically injury response and recovery after stroke with regard to different age groups, are needed. Infarct size and location of stroke appear to influence the level of neurologic deficits and eventual stroke outcomes e.g. left-hemispheric ischaemic strokes are more frequent and often have higher admission NIHSS scores as well as poorer survival than right-hemispheric counterparts.[309] However, few authors have attempted to unravel the relative role of these factors in the severity differences across the different patient groups including men and women, or young and older people. Recent advanced brain imaging undertaken to investigate neurological deficits among people with different stroke types may offer better opportunities to understand the sex and age differences in brain injury.[310,311] Also, female members are often excluded in the neuroscience experiments because of the hormonal fluctuations associated with the reproductive cycle.[312] A recent meta-analysis of neuroscience studies has shown that data from female rats are no more variable than data from males.[313] This suggests a need to include females in animal models to understand the sex difference in severity of stroke.[314]

The sex differences in stroke severity existed for IS but not ICH. The aetiology of IS include hypo-perfusion, embolism, or thrombosis whereas ICH could be caused by trauma, ruptured cerebral aneurysm, or arteriovenous malformation. More severe IS in women, as discussed above, can reflect a combination of such factors that differ between men and women as age, pre-stroke function, and other comorbidities. By contrast, the severity of ICH may vary by the size and location of haematoma, and

intraventricular extension and be dependent on cardiovascular risk factors.[315] Uncertainty exists over the sex differences in stroke severity among women and men with ICH,[316] requiring further research.

Our study has a number of strengths. To our knowledge, we have provided the first pooled estimates of sex differences in stroke severity, separately for IS and ICH. We compiled the IPD from eight population-based studies from various regions of the world. The use of two-stage method for meta-analysis of IPD allowed us to overcome some of the limitations that result from not all potential confounding factors being measured across all studies.[204] The data came from high-quality population-based studies free of the limitations of hospital-based or convenience samples and had a very large sample, making this study adequately powered to test our hypotheses.

However, limitations need to be acknowledged. The population-based studies in our research networks are mostly from high-income countries (7/8 studies), potentially leading to less generalizable results. We were unable to include 5 studies because NIHSS data were not available (Table e-1) thereby reducing the statistical power. The methods and sources of data collection differed across cohorts, and this may have contributed to the differing confounding variables identified between studies. In particular, our inability to detect whether IS subtypes confounded the association between sex and severity is likely attributable to the scarce data on IS sub-types (TOAST classification) which were only collected in 4 studies. Further research is needed to explore the role of the mechanism of IS on the sex difference in severity of stroke. There was a lack of data on subdomain scores of NIHSS, another potential contributor to the sex difference in severity of stroke. Although the rate of missing

data on NIHSS and covariates (<10%) was low enough that imputation of missing data was not required, we could not eliminate the possibility of some selection bias. Finally, the number of studies forming our pooled estimates was less than required (≥10) for the exploration of heterogeneity between studies using meta-regression.[231]

Conclusion

Women are more likely to present with severe IS than men and the difference is partly explained by their advanced age, greater pre-stroke functional limitation and presence of AF. Given these findings, strategies to improve pre-stroke health and access to evidence-based care for the elderly could help reduce differences in stroke severity between men and women. In addition, understanding the origin of more severe strokes in women compared to men should be a priority area for further research, more studies that attempt to identify other potential explanatory factors such as IS stroke mechanism, treatment of AF, and other comorbidities are needed.

Table 6-1. Details of eight included cohorts: baseline data on first-ever ischaemic stroke and intracerebral haemorrhage stroke

Study	Study year	Baseline, N	Among participants with NIHSS data							
			N	Women (%)	Mean age, years (SD)		Median NIHSS (IQR)		NIHSS>7, n (%)	
					Men	Women	Men	Women	Men	Women
Ischaemic stroke									(n=2,603)	(n=2,723)
Oxford, UK	‘02-‘13	1103	1087	49.4	**72.4 (12.0)**	**77.7 (12.1)**	**3 (1-6)**	**3 (1-9)**	**112 (20.4)**	**157 (29.2)**
Joinville, Brazil	‘09-‘14	1494	1494	47.8	**63.5 (12.5)**	**66.8 (15.7)**	**3 (2-8)**	**4 (2-11)**	**198 (25.4)**	**253 (35.4)**
Melbourne, Australia	‘96-‘99	921	744	52.0	**72.4 (12.7)**	**76.3 (14.3)**	4 (2-10)	5 (2-12)	**112 (31.4)**	**150 (38.8)**
Perth, Australia	‘00-‘01	140	123	50.4	74.0 (12.5)	78.0 (10.1)	5 (3-11)	6 (3-13)	21 (34.4)	26 (41.9)
Orebro, Sweden	‘99-‘00	274	274	54.4	**73.1 (10.5)**	**77.1 (10.7)**	**4 (2-6)**	**5 (3-10)**	**28 (22.4)**	**50 (33.6)**
Dijon, France	‘06-‘12	1238	1238	54.1	**71.7 (15.3)**	**77.2 (15.8)**	**4 (2-9)**	**4 (2-12)**	**170 (29.9)**	**248 (37.0)**
Mãtao, Brazil	‘03-‘04	68	67	38.8	65.1 (12.3)	64.5 (12.6)	**5 (2-11)**	**8 (5-10)**	12 (29.3)	13 (50.0)
Tartu, Estonia*	‘02-‘03	332	299	59.5	**68.1 (10.9)**	**75.6 (10.9)**	**5 (0-14)**	**9 (2-16)**	**44 (36.4)**	**97 (54.5)**
Summary estimate (95% CI)		5,570	5,326	51.6	**70.0 (67.4-72.6)**	**74.5 (72.0-77.2)**	4 (2-8)	4 (2-11)	**27.9% (24.1-31.9%)**	**38.6% (33.8-43.6%)**
ICH									(n=400)	(n=333)
Oxford, UK	‘02-‘13	112	94	48.9	69.5 (14.3)	73.5 (16.2)	7 (3-15)	7 (3-16)	22 (45.8)	22 (47.8)
Joinville, Brazil	‘09-‘14	223	223	42.2	**58.2 (15.4)**	**62.5 (15.5)**	17 (5-27)	17 (5-27)	86 (66.7)	66 (70.2)
Melbourne, Australia	‘96-‘99	191	136	49.3	**70.3 (13.5)**	**75.2 (15.2)**	**8 (3-20)**	**14 (5-27)**	39 (53.4)	47 (66.2)
Perth, Australia	‘00-‘01	19	13	46.7	68.0 (18.5)	73.5 (12.3)	9 (3-23)	15 (1-21)	4 (50.0)	5 (71.4)
Orebro, Sweden	‘99-‘00	44	44	43.2	71.9 (11.5)	75.6 (9.9)	9 (4-12)	10 (4-23)	15 (60.0)	12 (63.2)
Dijon, France	‘06-‘12	197	197	53.3	**71.0 (15.8)**	**76.6 (18.3)**	9 (4-22)	10 (4-22)	54 (58.7)	67 (63.8)
Mãtao, Brazil	‘03-‘04	12	11	27.3	62.9 (7.0)	68.7 (7.5)	18 (8-25)	32 (7-32)	6 (75.0)	2 (66.7)
Tartu, Estonia*	‘02-‘03	57	55	50.9	63.6 (15.9)	68.1 (12.6)	20 (5-25)	14 (7-25)	19 (70.4)	19 (67.9)
Summary estimate (95% CI)		855	773	48.3	67.0 (63.7-70.3)	71.7 (68.5-75.1)	10 (4-23)	12 (5-24)	60.9% (55.6-66.2%)	64.2% (59.3-68.9%)

ICH=Intracerebral haemorrhage; Bold denotes statistically significant results; NIHSS, National Institutes of Health Stroke Scale
*Stroke severity in Tartu study was mapped from Scandinavian Stroke Scale (SSS) to NIHSS (see Methods)

Table 6-2. List of factors contributing to the difference in stroke severity between women and men in multivariable models by stroke type (more severe stroke was defined as National Institutes of Health Stroke Scale >7)

Study	Ischaemic stroke		Intracerebral haemorrhage	
	N*	Actual confounders in the fully adjusted model	N*	Actual confounders in the fully adjusted model
Oxford	1077	age, pre-stroke mRS, AF	94	age‡
Joinville†	1494	age	223	age‡
Melbourne	647	age, pre-stroke Barthel, pre-stroke dementia	136	age‡
Perth	123	age	13	age‡
Orebro	274	age‡, institutional residence, AF	44	age‡
Dijon	1238	age, institutional residence, smoking	197	age‡
Mãtao†	67	age‡	11	age‡
Tartu	280	age, pre-stroke mRS	55	age‡
Pooled	5,200		773	

AF, atrial fibrillation; mRS, modified Rankin Scale

* the sample size were the same among the unadjusted model and fully-adjusted model

† data on pre-stroke dependency were unavailable

‡ age was selected to be forced into all the final fully-adjusted models regardless of meeting all 4 criteria (missing <20% of cases; associated with NIHSS; associated with sex, and changed the magnitude of the sex coefficient by ≥10%; see Methods)

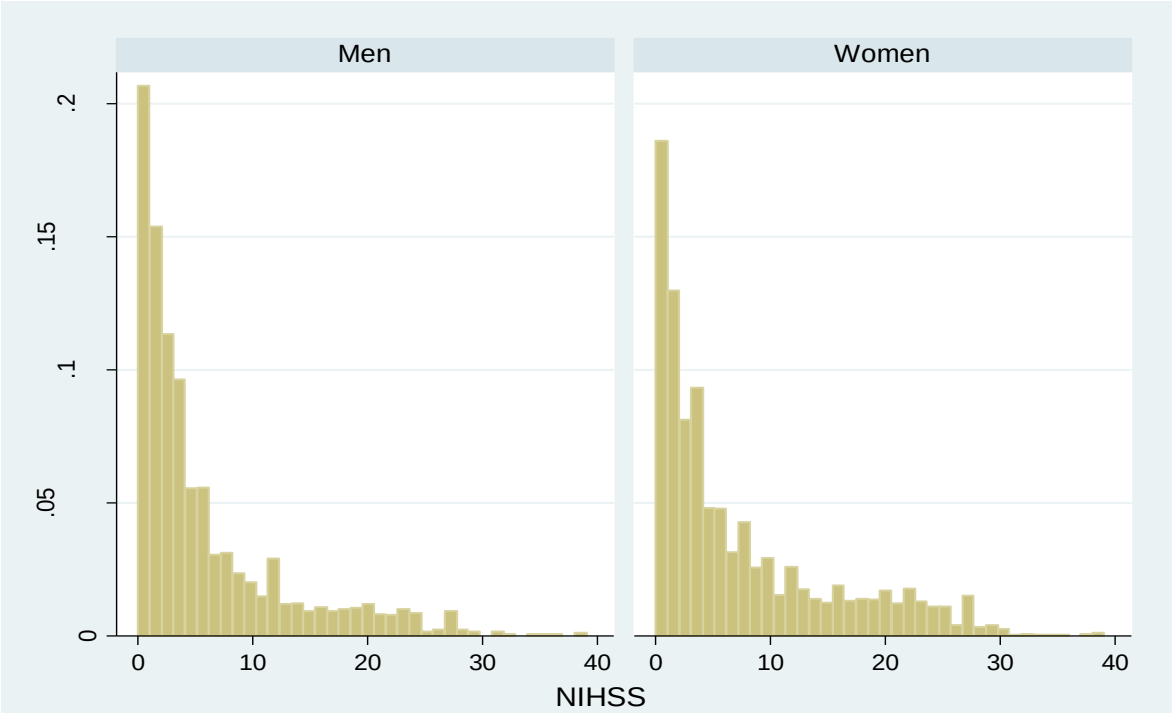
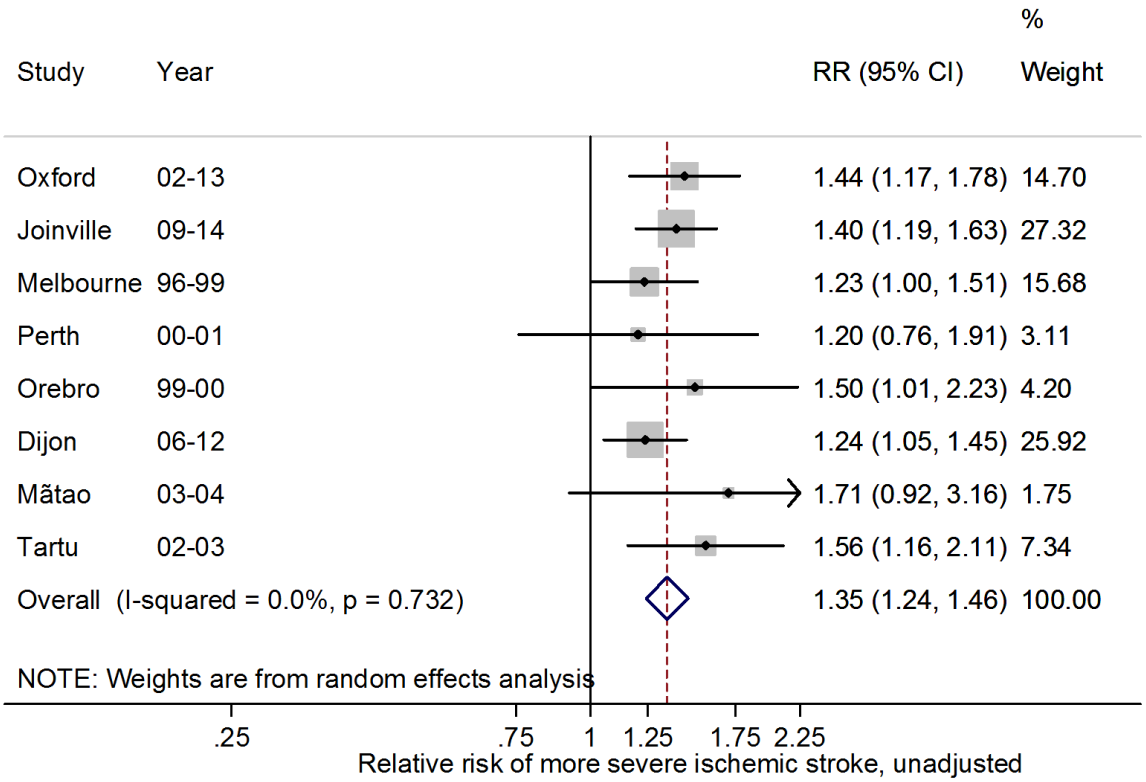


Figure 6-1. Distribution of the National Institutes of Health Stroke Scale (NIHSS) scores by sex among those with stroke (both ischaemic and intracerebral haemorrhagic stroke; n=6,099)



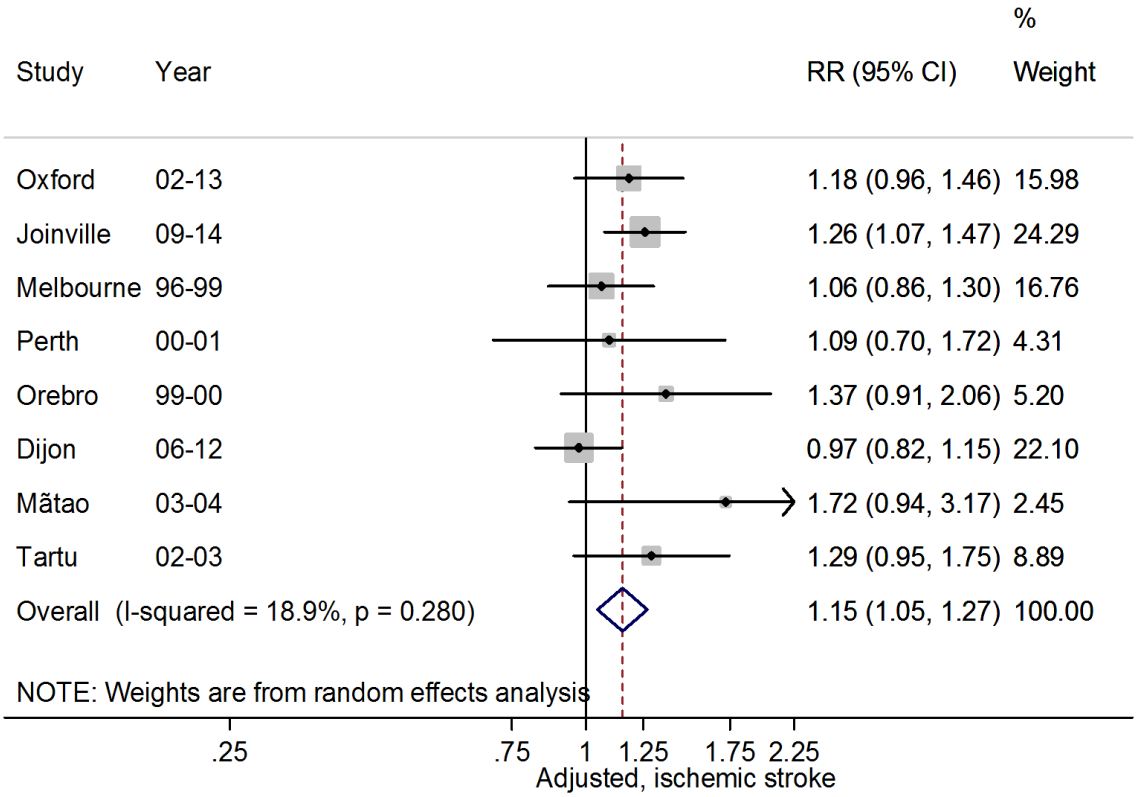
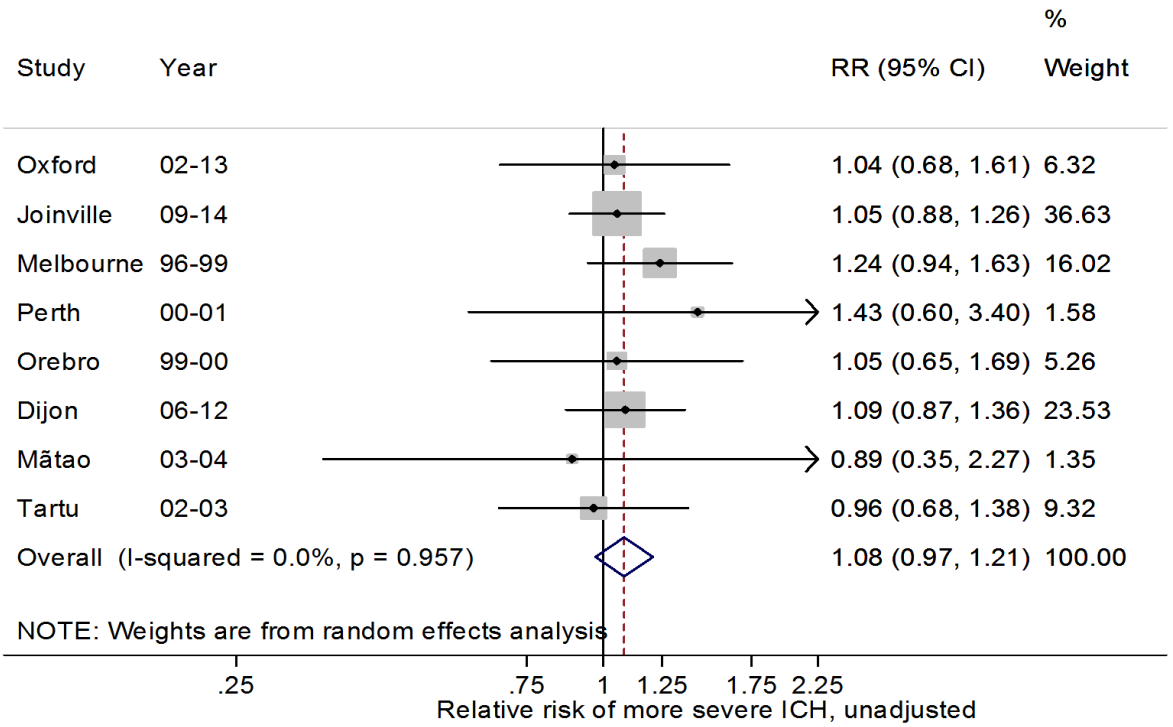


Figure 6-2. Difference in stroke severity between women and men with ischaemic stroke: unadjusted (top) and adjusted (bottom) random-effects meta-analyses. More severe stroke was defined as National Institutes of Health Stroke Scale >7.



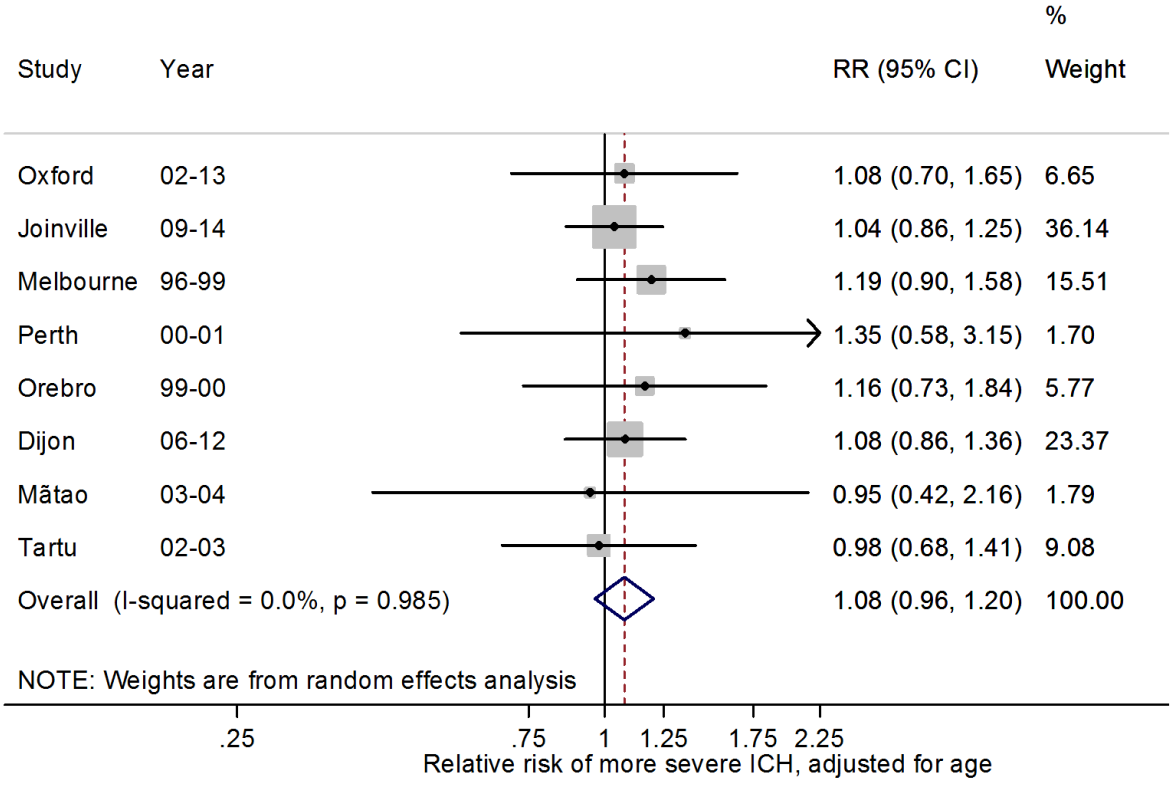


Figure 6-3. Difference in stroke severity between women and men with intracerebral haemorrhage (ICH) in unadjusted (top) and adjusted (bottom) random-effect meta-analyses. More severe stroke was defined as National Institutes of Health Stroke Scale >7.

Chapter 7: Methods related to Australian Stroke Clinical Registry (AuSCR) data collection and application in my research

7.1 Preface

In the second part of this thesis, I examined the differences between men and women in the receipt of processes of stroke care provided in hospital and associated patient outcomes using the data from the Australian Stroke Clinical Registry (AuSCR). This Chapter describes the background methods of the AuSCR including the study setting, participants, clinical and outcome variables, as well as patient characteristics.

Detailed information regarding the specific statistical methods for each research question are described in relevant chapters (**Chapter 8**: processes of care and 1-year mortality; **Chapter 9**: cause of death up to 1 year after stroke; **Chapter 10**: health-related quality of life at 3-6 months).

7.2 Ethics

This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0015287). My research proposal was also approved by the AuSCR Research Task Group and its Management Committee in August 2016 and its Management Committee in August 2016 to enable me to examine sex differences in acute hospital care and the relationship with patient outcomes up to one year after

stroke. Appropriate ethics and/or governance approvals were obtained for all participating hospitals in AuSCR and the Australian Institute of Health and Welfare (AIHW) to conduct data linkage to the National Death Index.

7.3 Study population and design

The AuSCR is a multicentre, prospective, nationwide registry designed to collect important patient data on the quality of acute stroke care and patient outcomes.[236] The AuSCR incorporates standardised methods of data collection using an online webtool data entry system with logic checks and data importing and exporting features.[317] The AuSCR was developed based on national operating standards and technical principals for clinical disease registries.[318] These principles are used to develop and evaluate the structure, governance and operations of Australian Clinical Quality Registries including the following categories: attributes of Australian Clinical Quality Registries, data collection, data elements, risk adjustment, data security, and ensuring data quality. Clinical (process of care) indicators obtained from the AuSCR are those prioritised as nationally relevant for stroke care as guided by the National Acute Stroke Clinical Guidelines that were prioritised as part of a consensus process.[319] All the variables available in the AuSCR, their definitions and data specifications are compliant with national and international electronic health data dictionaries and standards.[318] The detailed information on AuCR policies and data dictionary are available at the website: www.auscr.com.au.

Data quality assessments are undertaken regularly by the AuSCR Office staff to minimise missing data and to improve the reliability of data. Medical record audits

(i.e. 10% random audit at each new site) are conducted and the results of these audits are used to improve data quality by indicating areas for additional training or amendments to data dictionary items that are ambiguous.[317]

The AuSCR includes all consecutive acute stroke or transient ischaemic attack (TIA) admissions to participating hospitals that are identified by clinicians. The registry is based on an "opt-out" consent model, where patients are provided with information on the purpose of the registry and options to withdrawal their data.[320] Staff from participating hospitals enter patients' data at the acute stage in the web tool. Subsequently, AuSCR trained staff contact eligible patients between 90-180 days after the admission date to gather outcome data primarily by postal questionnaire and non-responders are followed-up by telephone.[321] Survival information is updated each year for the AuSCR participants through linking with national death registrations (the National Death Index) provided by the AIHW.[320]

Since 2009 when the registry was established, there has been an increasing number of patients registered (Figure 1). The AuSCR hospital data scaled up from 4 sites to 13 sites from mid-2009 to 2010. Now more than 70 hospitals have provided > 60,000 patient episodes, demonstrating the high level of participation from across Australia. The AuSCR was established to be used by a wide range of hospitals (i.e. public and private hospitals, children's hospitals and located in rural or urban areas) to ensure a representative sample of Australia's healthcare system and geography.[319]

This observational study included only first-ever cases of stroke registered in the AuSCR database between 2010 and 2014 including patients who completed followed-

up between 3-6 months and had their 1-year survival status determined through the data linkage program with AIHW. The dataset included more than 14,000 first-ever strokes admitted to 39 hospitals participating in the AuSCR across five states of Australia. The patient sample was consistent with other representative stroke populations.[236] However, patients registered in the AuSCR hospitals during the 2010-2014 period were mainly admitted to neurology/stroke units and from metropolitan areas,[236] and the possibility of bias is discussed in the following chapters. It should also be noted that cause of death (COD) data from the National Death Index – AIHW are updated annually while all other variables e.g. date of death are updated monthly.[320] The data on COD were only available in a subset of cases registered in the 2010-2013 AuSCR dataset, due to the lag times for COD data being available to the AIHW.

The AuSCR data user agreement specifies that data cannot be transferred to the University of Tasmania or saved on portable storage devices. In accordance with the data access policy, I undertook the data analyses at Monash University, Clayton in March and November 2017 under the supervision of Professor Dominique Cadilhac - the AuSCR data custodian and coordinating principal investigator. I was provided authorised de-identified AuSCR datasets held at Monash University on behalf of the Florey - Institute of Neuroscience and Mental Health (data custodial organisation).

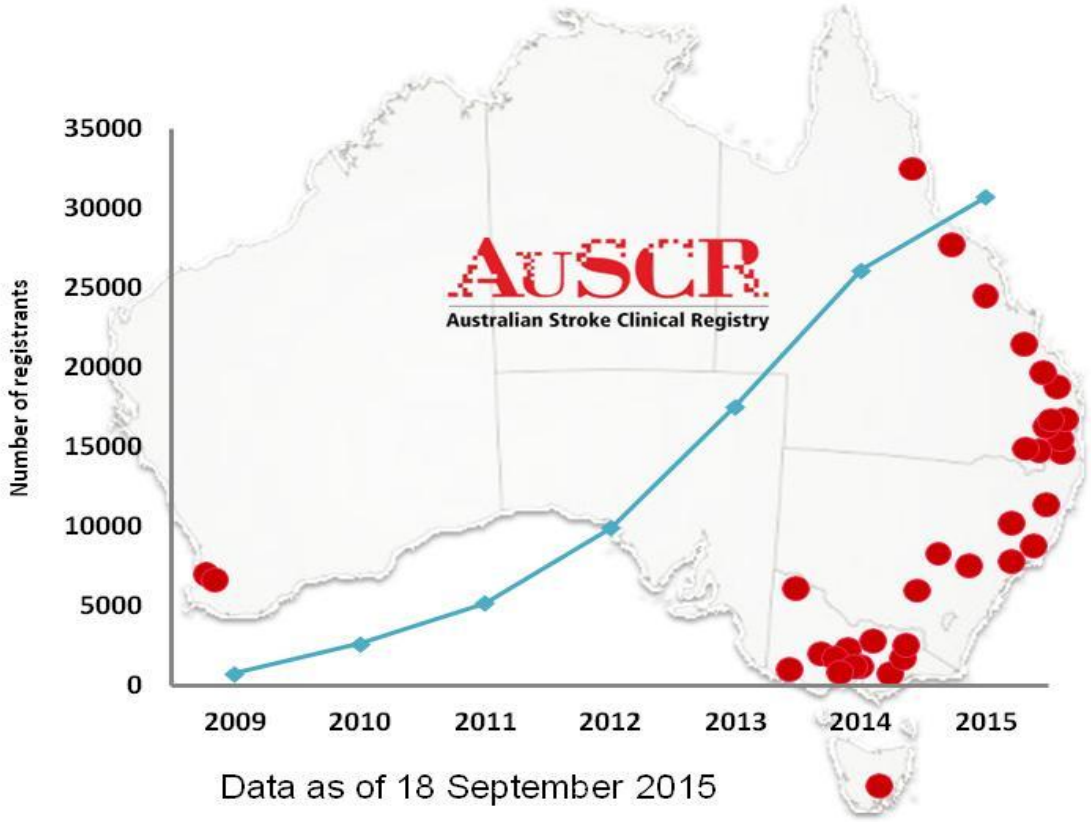


Figure 7-1. Number of registrant in the Australian Stroke Clinical Registry (AuSCR) with the data as of September 2015 (Source: the AuSCR report 2016)

7.4 Research questions

The research questions addressed in the part of thesis using the AuSCR data are highlighted below.

1) Are there differences between women and men in receiving evidence-based care and all-cause mortality at 1 year after stroke? What factors contribute to the sex differences in mortality?
2) Are there differences between women and men in causes of death and specific-cause of excess mortality up to 1 year after stroke? What factors, including the evidence-based care, contribute to the sex differences?
3) Are there differences between women and men in HRQoL up to 6 months after stroke? What factors contribute to the sex differences in HRQoL?

7.5 Study factors

Factors investigated were patient characteristics and care received in the hospital that might explain the sex differences in care or outcomes after stroke. These factors were categorised into five groups including (1) socio-demographics, (2) stroke-related factors, (3) discharge information, (4) evidence-based processes of care provided in the hospital, and (5) post-discharge stroke factors. These groups of factors are described in more detail below.

7.5.1 Socio-demographics

Sociodemographic factors included age, country of birth, ethnicity, state of residence (New South Wales, Queensland, Western Australia, Victoria, and Tasmania). Socioeconomic position was determined using the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) using patient residential postcodes at time of stroke.[322] The IRSAD information was presented as predetermined quintiles with a higher quintile indicating greater socioeconomic advantage.

7.5.2 Stroke-related factors

The ability to walk independently on admission was used as a proxy assessment of stroke severity. This simple indicator (one question) has been proven as a reliable predictor of stroke severity in the absence of severity scales such as the National Institute Health Stroke Scale (11 items).[323] Stroke type was categorised into three groups including ischaemic stroke, intracerebral haemorrhage and undetermined stroke. Information on the time from stroke onset to hospital arrival, and whether patients were transferred from another hospital were also collected.

7.5.3 Discharge information

The length of stay was counted as the date of discharge minus the date of admission. Discharge destination after the acute phase of stroke was categorised into the following groups: home (with or without support), residential aged care, inpatient rehabilitation, and other places (e.g. transfer to another hospital).

7.5.4 Processes of care

There are four processes of hospital care provided prioritised as nationally relevant [319,324] and are collected for all patients (n=39 hospitals): *access to stroke unit care, intravenous thrombolysis, care plan provided at discharge*, and being *discharged on antihypertensive agent(s)*.

Four additional processes of care were collected in the state of Queensland (n=21 hospitals) including: *mobilisation during admission, swallow screen, aspirin administration ≤48 hours* (among those with ischaemic strokes), and *being discharged on antiplatelets or antithrombotic medications* (ischaemic stroke).

7.5.5 Post-discharge stroke factors

Between 90 and 180 days after admission eligible AuSCR registrants (i.e. known to be alive and not previously followed up) were asked to self-report their current place of residence (i.e. *high-level residential care, low-level residential care, home with supports, home without supports, rehabilitation, transitional care service, hospital, and other)* and living arrangements *(whether the registrant lives alone).* The presence or absence of a recurrent stroke event (not including TIA) and readmission since discharge (i.e. readmission date and reasons) were also self-reported by the registrants or their next-of-kin/key contact person.

7.6 Study outcomes

7.6.1 Mortality outcomes

Survival up to one year after stroke was obtained from patient-level data linkage to national death registrations by the AIHW. One-year COD based on ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) codes were classified into: stroke, ischaemic heart disease, other cardiovascular disease (e.g. hypertensive diseases, atrial fibrillation), cancer, and other causes. As mentioned earlier in section **7.3**, only a subset of cases registered in the AuSCR between 2010 and 2013 were included in my COD analyses.

7.6.2 Health-related quality of life (HRQoL)

HRQoL was assessed using the European Quality of Life–5 Dimensions (EQ-5D-3L) instrument.[194] Participants in the registry were contacted between 90 and 180 days after the index event by post or telephone.[236] For each of the 5 dimensions of the EQ-5D including mobility, self-care, usual activities, depression/anxiety, and pain), there are three response categories: no problem, some/moderate, and extreme problem.

EQ-5D information was collected from patients or proxy respondents when patients were unable to respond the interviewers. The proxy response to the EQ5D questionnaire at 6 months after stroke has an acceptable reliability that can substitute for missing of patient assessment.[325] Unassessed survivors included those were lost to follow-up only after multiple contact attempts (non-responders) and those for which

the time from discharge was more than 6 months or the patient/proxy refused (non-consenters).

7.6.3 General information regarding my analytical process and AuSCR data quality

I performed the data analyses under the supervision of Prof Cadilhac using the prepared dataset from a dedicated folder stored on the Monash University secure share drive. The de-identified dataset and relevant coding files were provided in Stata programs (version 12.1; StataCorp Texas, 2011)[269] with variables derived from AuSCR publications and reports to ensure consistency in estimates from these data. The only new variable I derived, with the assistance of a staff at Monash, is the COD categories. Only data outputs and summary estimates from Stata programs were exported for manuscript preparation.

Data clean was undertaken by Monash staff to ensure data quality. The AuSCR dataset has generally very low rate of missing data on covariates (i.e. <10% for almost all baseline factors). The linkage of survival status to national death registrations was used to minimise the possibility of bias of missing data. Detailed information regarding the missing data on covariates and outcomes are described in relevant chapters.

Chapter 8: Sex differences in care and long-term mortality after stroke: Australian Stroke Clinical Registry (AuSCR)

8.1 Preface

At the time of submission of this thesis, the contents of this chapter have been under review following request for revisions from the *Journal of Women's Health.*

Phan HT, Gall SL, Blizzard CL, Lannin N, Thrift AG, Anderson CS, Kim J, Grimley R, Castley HC, Hand P, Cadilhac D. Differences in stroke care and outcomes after stroke for women compared to men: Australian Stroke Clinical Registry (AuSCR). Sex differences in care and long-term mortality after stroke: Australian Stroke Clinical Registry (AuSCR).

8.2 Abstract

Introduction: There is some evidence that women receive evidence-based care less often than men, but how this influences long-term mortality after stroke is unclear. We determined this issue using data obtained from a national stroke registry.

Methods: Data are first-ever hospitalised strokes (2010-2014) in the Australian Stroke Clinical Registry from 39 hospitals linked to the national death registrations. Multilevel Poisson regression was used to estimate the female:male mortality rate

ratio (MRR), with adjustment for socio-demographics, stroke type, severity, discharge disposition, and processes of care (stroke unit care, intravenous thrombolysis, antihypertensive agent[s] and discharge care plan).

Results: Among 14,118 events (46% females), women were 7 years older and had greater baseline severity compared to men (29% vs 37%; p<0.001), but there were no sex differences in the four processes of care available across hospitals. Analyses of additional processes from Queensland hospitals (n=5,224) revealed that women were less often administered aspirin ≤48 hours than men (51% vs 58%, p<0.014). In the whole cohort, 1-year mortality was greater in women than men ($MRR_{unadjusted}$ 1.44, 95% CI 1.34-1.54). However, there were no significant sex differences after adjusting for age and stroke severity ($MRR_{adjusted}$ 1.05, 95% CI 0.98-1.14). In Queensland hospitals, older age, severity, and under-treatment with aspirin contributed to the sex differences in mortality.

Conclusion: Greater mortality in women can be explained by differences in age and stroke severity. This highlights the importance of better management of risk factors in the elderly and, potentially, the need for greater access to early aspirin for women with stroke.

8.3 Introduction

In many countries, the total burden of disease attributed to stroke is greater in women than men.[326] Women, in comparison to men, have also been reported to have worse outcomes after stroke including greater mortality,[236] worse functional outcomes,[24] and

poorer health-related quality of life.[24] Some investigators in the United States and Europe have found that women receive evidence-based care less often than men.[80,84] However, whether disparities in stroke care account for differences in outcome between men and women has not been fully examined.[327]

In our recent meta-analysis of individual participant data obtained from population-based studies, women received carotid investigations and echocardiography less often than men.[236] Women had 35% greater mortality at 1 year after stroke compared to men. The difference in mortality was largely due to advanced age, more severe stroke, functional limitation before stroke and the presence of atrial fibrillation in women, rather than differences in care.[236] Although these findings were insightful, they were limited by the fact that the data on processes of care were scarce and outdated. There is a need to explore sex differences in care and outcome in contemporary datasets.

The purpose of this study was to use contemporary data from the Australian Stroke Clinical Registry (AuSCR) to examine (1) sex differences in access to evidence-based processes of care and mortality outcome in people admitted to hospital with acute stroke in Australia; and (2) identify the factors including evidence-based stroke care that may account for any differences in mortality between men and women up to 1 year after stroke.

8.4 Methods

As a nationwide, multicentre, prospective registry, the AuSCR incorporates standardised methods of data collection for important processes of stroke care in

Australia.[236] In this study, we included first-ever cases of stroke admitted to 39 hospitals participating in the AuSCR between 2010 and 2014. This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0015287). Our research proposal was also approved by the AuSCR Research Task Group and its Management Committee in August 2016. Appropriate ethics and/or governance approvals were obtained for all participating hospitals in AuSCR and the Australian Institute of Health and Welfare to conduct data linkage to the National Death Index.

8.4.1 Study factors

Central to the aims of the study was the examination of a wide range of factors assessed in the AuSCR registry that might explain the sex differences in mortality after stroke, including patient characteristics and care received in hospital. Factors investigated included (1) socio-demographics: *age, country of birth, state of residence* (New South Wales, Queensland, Western Australia, Victoria and Tasmania), and *socioeconomic position* determined using the Index of Relative Socio-Economic Advantage and Disadvantage;[322] (2) stroke-related factors: *stroke severity (indicated by walking ability on admission),*[236,328] *stroke type* (ischaemic, intracerebral haemorrhage and undetermined stroke), *cause of stroke known, time from stroke onset to hospital arrival, and whether patients were transferred from another hospital*; (3) discharge information: *length of stay and discharge destination*; and (4) evidence-based processes of care provided while in hospital. Of note, data on pre-stroke function were unavailable in the AuSCR dataset. The ability to walk independently on

admission was used as a proxy assessment of stroke severity. AuSCR did not collect data on people with subarachnoid haemorrhage (SAH).[319] Systemic recording of cause of ischemic stroke known was defined according to the Acute Stroke Treatment (TOAST) criteria.[299] The TOAST classification includes different mechanisms of ischemic stroke including large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and other determined aetiology (i.e. haemorrhage) that would be applicable to all types of stroke. For further details the AuSCR data dictionary is available online www.auscr.com.au.

Data on processes of care obtained from the AuSCR were those prioritised as nationally relevant:[319,324] *stroke unit access, intravenous thrombolysis, care plan provided at discharge*, and being *discharged on antihypertensive agent(s)*. Four additional processes of care were collected in the state of Queensland (n=21 hospitals) including: *mobilization during admission, swallow screen, aspirin administration ≤48 hours*, and *being discharged on antiplatelets or antithrombotic medications* (ischaemic stroke).

8.4.2 Outcome measurement

Survival up to one year after stroke was obtained from patient-level data linkage to national death registrations undertaken by the Australian Institute of Health and Welfare.

8.4.3 Statistical analysis

Statistical analyses were performed using Stata 12.1 (StataCorp Texas, 2011).[269] All two-tailed p-values ≤0.05 were considered statistically significant. Multilevel random-effects log-binomial regression, accounting for individual hospital clusters, was used to generate prevalence ratio (PR) of the sex difference in discharge information and processes of care provided while in hospital.

Multilevel Poisson modelling, accounting for the hospital as a unit of patient clusters, with sex-specific person-days of follow-up entered as an offset, was used to estimate the mortality rate ratio (MRR) for women compared to men at 7, 30 days, and 1 year after stroke. To assess the role of covariates on the association between sex and each outcome, we used purposeful model building.[207] Variables were entered into the model only if they met all three criteria that defined them as potential confounders[207] (**Supplemental Methods**: **section 8.7.1**). The model-building process was initially undertaken for each variable separately and then adjustment for all significant confounding factors were examined in multivariable models. The modifying effect of a covariate on the sex difference was assessed by a test of the statistical significance of the coefficient of a sex × covariate product term.

Estimates of the sex differences in processes of care and mortality after stroke were performed for all hospitals (4 indicators) and in the Queensland subset that had more detailed information on stroke care (4 additional indicators). In the relevant subgroups, we examined whether any factors related to processes of care that showed a sex difference were confounders of the association between sex and mortality (**Supplemental Methods**: **section 8.7.1**). Some medication restrictions may be

appropriate given contraindication or to meet treatment guidelines.[324] We took these into account when examining aspirin administration in the subset of Queensland patients. For those without aspirin ≤48 hours we examined whether the person: (1) died ≤48 hours, (2) received thrombolysis therapy, and (3) received antiplatelet or antithrombotic therapy at discharge.

To investigate the effect of missing data on confounding factors in predictive models, multiple imputation using chained equations[206] (n=50 imputations) was performed. Estimates from imputed results based on valid data on outcome and covariates were then compared with complete-case results. Sensitivity analyses were used to examine the effect of excluding earlier deaths after stroke where possible (e.g. 7 days), and any differences in patient characteristics or quality of care between Queensland and non-Queensland hospitals on the results. We also considered a further analysis of the sex difference in mortality among a subset of those with admission time ≤3.5 hours potentially eligible for early thrombolytic therapy. We assumed that those presenting at hospital ≤3.5 hours of stroke onset needed about one additional hour for decision processes to occur to be eligible for treatment (≤4.5 hours after acute ischaemic stroke).

8.5 **Results**

In the whole cohort, there were 14,118 patients experiencing first−ever stroke between 2010 and 2014, with 81% being ischaemic and 46.3% female. Median age of stroke was 75 years (Interquartile range 64-84). Compared to males, female registrants, based on sociodemographic and stroke-related characteristics, were 7

years older (median age: 79 vs 72 years; p<0.001), and less able to walk independently on admission (indicating more severe strokes; female 28.7% vs male 37.0%, p<0.001; **Table 8-1**).

Sex difference in processes of care and discharge information

There were no statistically significant differences between men and women in the provision of stroke best practice care, with the exception of, in the subset of Queensland data, women being less often administered aspirin ≤48 hours than men (60.8% vs 68.9%, p=0.015; **Table 8-2**). Sensitivity analyses (excluding patients who died ≤48 hours or received intravenous thrombolysis) did not change this finding whereby there was less frequent use of aspirin ≤48 hours in women than men (**Appendix E**: **Supplemental Table E-1**). The observed difference between men and women receiving early aspirin was attenuated after accounting for age and stroke severity (female:male prevalence ratio, $PR_{unadjusted}$ 0.91, 95% CI 0.85-0.98; $PR_{adjusted}$ 0.94, 95% CI 0.87-1.02; **Table 8-3**).

Slightly fewer women in the whole cohort appeared to receive thrombolysis therapy compared to men, but the difference was only apparent when stroke severity was taken into account ($PR_{unadjusted}$ 0.98, 95% CI 0.94-1.02; $PR_{fully\text{-}adjusted}$ 0.91, 95% CI 0.82-1.02). Analyses of a subset of patients (n=4695; 44% being female) potentially eligible for thrombolysis (admission time ≤3.5 hours) showed that women and men were equally given the therapy ($PR_{unadjusted}$ 1.07, 95% CI 0.96-1.20; $PR_{fully\text{-}adjusted}$ 1.03, 95% CI 0.92-1.14 (**Table 8-3**).

When compared to men, women were more often discharged to aged care (6.8% vs 3.0%; p<0.001), and less often discharged directly home from acute care (34.1% vs

42.5%; P<0.001, **Table 8-2**). Adjustment for age and severity substantially attenuated the association between sex and discharge destination (**Table 8-3**).

Sex difference in mortality after stroke

In the whole cohort, the case fatality rate at 7, 30 days and 1 year was greater for women compared to men (**Figure 8-1**). In univariable analyses, significant contributing factors to the sex difference in mortality up to 1 year after stroke were age, stroke severity, and discharge destination (being discharged home or to aged care; **Supplemental Table E-2**).

In the best fit multivariable model, data were available for 94% (n=13,304) of 14,114 cases because of missing data on confounding factors. Women were approximately 40% more likely to be deceased after acute stroke compared to men in unadjusted analysis ($MRR_{unadjusted}$ 7-day 1.42, 95% CI 1.25-1.60; 30-day 1.45, 95% CI 1.33-1.59; 1-year 1.44, 95% CI 1.34-1.54; **Figure 8-2**). None of the four processes of care available for all hospitals confounded the association between sex and mortality both in the short and long term after stroke. Older age at stroke onset in women, compared to men, explained about 50-63% of their greater short-term mortality ($MRR_{age\text{-}adjusted}$ 7-day 1.19, 95% CI 1.05-1.35; 30-day 1.15, 95% CI 1.05-1.27; **Supplemental Table E-2**). Separate adjustment for stroke severity reduced the sex difference by 31-39% ($MRR_{severity\text{-}adjusted}$ 7-day 1.24, 95% CI 1.09-1.40; 30-day 1.29, 95% CI 1.18-1.41; **Supplemental Table E-2**). In the multivariable final model with adjustment for age and severity, there was no longer a significant difference between men and women in 7-day mortality ($MRR_{fully\text{-}adjusted}$ 7-day 1.09, 95% CI 0.96-1.24; 30-day 1.07, 95% CI

0.97-1.17; **Figure 8-2**). There was no evidence ofstatistical interactions between sex and covariates on the short-term mortality.

Importantly, stroke severity modified the sex difference in 1-year mortality after stroke ($P_{interaction}$=0.028). Among those able to walk at admission, age explained most of the excess deaths after stroke by women ($MRR_{unadjuted}$ 0.99, 95% CI 0.80-1.22; $MRR_{age\text{-}adjusted}$ 0.81, 95% CI 0.65-1.00; **Figure 8-3**). For those unable to walk, there was an excess of deaths after stroke in men that was only apparent when the generally younger age of the men was taken into account ($MRR_{unadjuted}$ 1.36, 95% CI 1.26-1.47; $MRR_{age\text{-}adjusted}$ 1.05, 95% CI 0.97-1.14; **Figure 8-3**).

Analyses of additional processes of care

Analyses of additional processes of care from Queensland patients (n=5,224) provided consistent results with mortality up to 1 year being greater in women than men ($MRR_{unadjusted}$ 30-day 1.26, 95% CI 1.26-1.47; 1-year 1.32, 95% CI 1.17-1.49; **Table 8-4**). Age and severity of stroke also contributed to the difference in mortality ($MRR_{adjusted}$ 30-day 0.89, 95% CI 0.76-1.03; 1-year 0.90, 95% CI 0.79-1.01; **Table 8-4**). There was no evidence of statistical interactions between sex and covariates on mortality up to 1 year after stroke. In a subgroup analysis restricted to only patients with ischaemic strokes, coupled with age and severity, a lesser proportion of aspirin administration in women also contributed to the sex difference in mortality ($MRR_{unadjusted}$ 30-day 1.45, 95% CI 1.19-1.76; 1-year 1.50, 95% CI 1.24-1.82; $MRR_{fully\text{-}adjusted}$ 30-day 0.87, 95% CI 0.72-1.07; 1-year 0.92, 95% CI 0.75-1.12; **Table 8-4**). Other sensitivity analyses to examine the effect of the multiple imputation to account for missing data, early deaths after stroke (e.g., 7 days) and, in a subset of

Queensland hospitals revealed that our findings were robust (**Supplemental Results**: section **8.7.2**, and **Appendix E**: **Supplemental Tables E-3** to **E-5**).

8.6 **Discussion**

We found that women generally had greater mortality up to 1 year after stroke compared to men in unadjusted analyses. The sex difference was largely attributable to advanced age and more severe strokes in women rather than differences in care provided while in hospital, confirming our previous findings in population-based studies.[236] These findings support the essential need of accounting for age and severity in reporting outcomes in stroke research,[329] especially sex-specific findings. There were no statistically significant sex differences in the provision of care except that fewer women received aspirin in hospital relative to men. The contribution of undertreatment with early aspirin in women to the sex difference in mortality after stroke is concerning and requires further investigation.

The present study provides additional evidence for the current literature on sex differences in stroke care and outcomes. Findings of this study suggest conflicting results compared to the US and European studies[61,126,145,330] that show no significant sex differences in stroke presentation and treatment, in both unadjusted and adjusted analyses. The discrepant findings among different studies may reflect differences in the study populations or variations in practice among regions.

Age was the most important factor contributing to the greater mortality after stroke in women compared to men. Older age at stroke onset may explain greater mortality for

several reasons including that elderly people usually present with more severe strokes and more comorbidities (e.g. atrial fibrillation–AF, hypertension and diabetes) which are associated with greater fatality after stroke.[15] Older adults may not receive evidence-based stroke care,[214] which may also be associated with their poorer outcome after stroke or may indicate the patient and their family's preference to avoid active treatment as part of end-of-life care. However, the perspectives of end-of-life care are rarely recorded in current stroke studies and differences by sex have not been explored. Irrespective of age or sex, further investigations are needed to identify the needs of palliative and end-of-life care in order to provide adequate care and support for stroke patients and their families.[331,332]

More severe strokes in women compared to men also contributed to their poorer outcome. This suggests that the sex difference could be attenuated by targeting modifiable factors contributing to stroke severity e.g. hypertension,[244] embolic stroke mechanism,[295] and AF.[245] Walking ability was used as a proxy for stroke severity.[60,328] The relative importance of these factors to differences in severity between women and men remains uncertain[84] because stroke severity is less often investigated as a separate endpoint. Further research is required to identify potential contributors to any observed sex difference in stroke severity. The ability to walk at admission, in this study, accounted for up to 39% of the sex difference in mortality. These findings are consistent with our meta-analysis of population-based studies whereby 51% of the sex difference was explained by stroke severity assessed using other instruments (e.g. NIHSS).[236] This suggests that although other stroke severity scales have more favourable construct validity this simple measure of walking ability

is reliably collected and serves as a good marker of stroke severity.[329] The study results corroborate the findings of previous work suggesting that the sex differences in mortality following stroke are mostly accounted by age and stroke severity.[236] However, accounting for age did not fully explain the sex difference in stroke severity. Potential reasons for the residual difference could be associated with sex differences in comorbid diseases[5] or the localization of brain function,[226] but further investigation is needed.

Importantly, greater mortality after stroke from women in Queensland could also be explained by the sex difference in aspirin administration ≤48 hours, a treatment that has strong evidence for reducing poor outcomes after stroke.[319] One explanation could be the greater presence of AF among women compared to men, with women therefore receiving anticoagulants instead of aspirin.[333] Aspirin may be withheld for >48 hours in cases experiencing haemorrhagic conversion after ischemic stroke, which may be either spontaneous or, occasionally a complication of thrombolytic therapy. However, this is likely to be a few cases. We were unable to examine these possibilities due to a lack of data on comorbidities and prescription of anticoagulant agents. Since 2017, the AuSCR recording guidance for aspirin collections has been modified with further options on reasons for not given the medication including contraindication and other antithrombotic agent provided. These data would be helpful for future studies to further examine the lower administration of aspirin in women with stroke compared to men. We did find some evidence that women who did not receive aspirin ≤48 hours were not receiving antiplatelet/anticoagulants at discharge (**Supplemental Table E-1**), which is in line with previous observations reporting the underuse of

antiplatelet/anticoagulants in women.[334] Another possibility of undertreament in women, given their advanced age when having a stroke, is the impact of multimorbidity and polypharmacy in older adults[335] but this is beyond the scope of this paper. The undertreatment with aspirin may also reflect worse health before stroke in women or contraindications to treatment such as allergy, bleeding disorder, or uncontrolled hypertension.[336] Further quantitative and qualitative research must be conducted to explore the reasons behind the under-treatment of aspirin in women and whether there are potential links between sex, age and medication prescription decision-making.

Although there was no evidence of a statistically significant difference between sexes, in the whole cohort, slightly fewer women received thrombolysis therapy than men. Patients with more severe stroke symptoms (unable to walk) are more likely to receive thrombolysis therapy (16.8% vs 5.3%, $p<0.001$), consistent with previous findings.[337] In the whole cohort, slightly fewer women received thrombolysis therapy than men and, therefore, adjustment for severity strengthened the association between sex and the receipt of thrombolysis (**Table 8-3**). In the present study, there was no detectable sex difference in the time from stroke onset to arrival or the proportion of those admitted to the hospital ≤3.5 hours (women 53.4% vs men 52.0%). However, due to the high percentage of missing data on admission time (22%, slightly greater for women), we suspect that there may be a role of delayed hospitalisation on the association between female sex and the lower receipt of intravenous thrombolysis. This could explain the findings that removing the delayed hospitalisation reversed the direction of sex difference. In the subset of patients with admission time ≤3.5 hours,

slightly more women were treated with thrombolysis therapy than men and, thus, the association became weaker after accounting for stroke severity (**Table 8-3**).

Several strengths should be acknowledged. These analyses are based on a large dataset from five states across Australia with a standardised collection to ensure data quality and adequate power to test our hypothesis. The possibility of bias of missing data could be minimised thanks to the linkage of survival status to national death registrations, very low rate of missing data on confounding factors and minor change in estimates from sensitivity analyses that replaced missing data using multiple imputation.

A number of limitations need to be considered. Some potential factors contributing to the sex difference in stroke care and long-term outcomes of stroke were not available in this registry. These include pre-stroke health, depression after stroke, history of comorbidities e.g. cardiovascular diseases, lifestyle behaviours and post-stroke depression. Our analyses were limited by the lack of information on whether the patient was living in institution (i.e. nursing home) or having functional limitations before stroke. Except for functional limitation before stroke and the presence of AF, we did not find these above factors were important in a previous study using data from population-based studies.[236] In future research will be able to use liked hospital administrative data to obtain comorbidity information (i.e. AF, diabetes, Charlson or Elixhauser Comorbidity Index) to enhance the data available from the AuSCR cohort.[338,339]

The majority of hospitals participating in AuSCR were those with well-developed systems of care for stroke whereby our estimates of in-hospital care processes were different from those provided by a wider range of hospitals. This might limit the generalizability of the results of the study. For example, according to the National Acute Audit Report 2015,[340] only 58%-67% patients accessed stroke units (2013-2015) and 7% of patients with ischemic stroke received intravenous thrombolysis (2013). The corresponding figures were 80% and 12%, respectively in the AuSCR. Although we found very little difference between men and women in the processes of care in the AuSCR, it is possible that there may be sex differences among non-AuSCR hospitals. Nevertheless, this is unlikely to substantially affect our conclusion that the sex differences in mortality were mostly explained by advanced age and stroke severity rather than a sex bias in stroke care.

The hospital-based design might under- or over-estimate the sex difference in mortality compared to population-based studies. This is because women tend to be older, live alone[94] or reside in an institution at time of stroke onset and may be less often admitted to hospital than men.[29] Among population-based stroke incidence studies, the admission rate varied by regions and study year, ranging from 79% in Perth (1989-1990),[341] 91% in Melbourne (1996-1999)[236,342] to as high as 96% in Adelaide (2009-2010).[343] Also, the proportion of neuroimaging performed during admission among population-based studies was at 80% for Perth,[341] 88% for Melbourne[344] to 95% for Adelaide.[343] The latter figure does not greatly differ from that of the nationalacute audit data from 2013-2015 whereby up to 96% of hospitalized people with stroke were given a brain imaging with only a 2% difference

between urban and rural areas.[345,346] These above figures suggest the selection bias from hospital-based studies is becoming minimal.

Our findings from the additional information on management of stroke from Queensland hospitals may be important to evaluate in the whole registry. Since mid-2016, all AuSCR hospitals have been able to expand the collection of these processes of care.

Conclusions

Women, compared to men, were older at stroke onset, less likely to walk on admission, less often treated with aspirin, more often discharged to aged care and more likely to be deceased up to 1 year after stroke. The greater mortality after stroke in women was explained by their advanced age, and more severe stroke. There was some evidence that under-treatment with aspirin in women further accounted for the sex differences in mortality. These findings highlight the importance of better management for high-risk individuals including those with more severe strokes and the elderly. This study using a national registry with stroke performance indicators aligned with current recommendations provides a greater understanding of the sex differences in the quality of care and outcomes to inform future work to address these differences.

Table 8-1. Characteristic of AuSCR registrants for first−ever stroke during 2010−2014 by sex

	Men	Women	P−value*
	n (%)	n (%)	
Number of cases	7580 (53.7%)	6538 (46.3%)	**<0.001**
Sociodemographics			
Age, median (IQR)†	71.9 (61.6−80.9)	78.6 (67.2−85.8)	**<0.001**
State†			
New South Wales	1486 (19.6%)	1166 (18.2%)	0.304
Queensland	2819 (37.2%)	2405 (36.8%)	
Tasmania	351 (4.6%)	296 (4.5%)	
Victoria	2613 (34.5%)	2432 (36.7%)	
Western Australia	311 (4.1%)	239 (3.6%)	
Born in Australia†	4805 (63.4%)	4419 (67.6%)	**0.005**
Aboriginal/Torres Strait Islander†	103 (1.4%)	103 (1.6%)	0.606
Socioeconomic status†			
IRSAD1 (most disadvantage)	1411 (18.6%)	1154 (17.7%)	0.931
IRSAD2	1568 (20.7%)	1354 (20.7%)	
IRSAD3	952 (12.6%)	814 (12.5%)	
IRSAD4	1528 (20.2%)	1312 (20.1%)	
IRSAD5 (least disadvantage)	2119 (28.0%)	1904 (29.1%)	
Stroke−related factors			
Transfer from other hospital†	1167 (15.5%)	873 (13.4%)	**0.005**
In−hospital stroke†	398 (5.3%)	376 (5.8%)	0.539
Time (minutes) from onset to arrival, median (IQR)§	192 (81−710)	184 (81−642)	0.178
Admission time ≤3.5 hours of symptom onset§	3083 (52.0%)	2721 (53.4%)	0.268
Walking independently at admission‡	2808 (37.0%)	1873 (28.7%)	**<0.001**
Type of stroke			
Intracerebral haemorrhagic	1185 (15.6%)	1049 (16.0%)	0.434
Ischaemic stroke (IS)	6174 (81.5%)	5270 (80.6%)	
Undetermined (not including subarachnoid haemorrhage)	218 (2.9%)	219 (3.4%)	
Cause of stroke known (IS only)†| |	3723 (50.5%)	3043 (47.9%)	**<0.001**

IRSAD: Index of Relative Socio-Economic Advantage and Disadvantage
* random−effects multilevel model allowing hospital clustering
† missing data <1%
‡ missing data <6%
§ missing data <22%
\| \| defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification

Table 8-2. Processes of care and discharge information of AuSCR registrants for first−ever stroke during 2010−2014

	Men n (%)	Women n (%)	P−value
Number of cases	7580 (53.7%)	6538 (46.3%)	**<0.001**
Evidence−based therapies			
Treated in stroke unit	6256 (82.5%)	5257 (80.4%)	0.259
Intravenous thrombolysis*	767 (12.5%)	632 (12.1%)	0.458
	767 (29.8%†)	632 (27.4%†)	0.181
Discharged on antihypertensives	4818 (70.9%)	3945 (70.2%)	0.555
Care plan on discharge to community	1828 (53.1%)	1368 (51.3%)	0.371
Discharge information			
Discharge destination			
Died in hospital	658 (8.7%)	780 (11.9%)	**<0.001**
Aged care	225 (3.0%)	441 (6.8%)	
Home	3220 (42.5%)	2226 (34.1%)	
Rehabilitation	2297 (30.3%)	2023 (31.0%)	
Hospitals/other	1180 (15.6%)	1068 (16.3%)	
Length of stay‡, median (IQR) days	5 (3−9)	6 (3−11)	**<0.001**
Additional indicators (Queensland data)			
Number of cases	2819 (54.0%)	2405 (46.0%)	**<0.001**
Mobilisation ≤48 hours§	857 (53.6%)	764 (49.0%)	0.211
Received swallow assessment ≤24 hours	1530 (54.3%)	1226 (50.1%)	0.458
Aspirin administration ≤48 hours*	1639 (68.9%)	1230 (60.8%)	**0.015**
Discharged on antiplatelets/antithrombotic*	1678 (81.0%)	1282 (76.7%)	0.442

Missing data on evidence-based therapy were assumed to be 'unreceived'
* among ischaemic strokes
† among those with admission time ≤3.5 hours
‡ among those discharged
§ if unable to walk on admission

Table 8-3. Prevalence ratio (PR)* of having more severe stroke, being discharge home or to aged care and receiving acute evidence−based therapies for women compared to men

	N	Unadjusted PR (95% CI)	Adjusted PR (95% CI)	Notes
Characteristics				
Able to walk on admission	13305	**0.78 (0.73, 0.82)**	**0.83 (0.78, 0.88)**	age
Discharged home	11646	**0.84 (0.79, 0.88)**	**0.94 (0.88, 0.99)**	age, severity
Discharged to aged care	11646	**2.40 (2.03, 2.83)**	**1.48 (1.25, 1.76)**	age, severity
Evidence−based care†				
Intravenous thrombolysis	10714	0.96 (0.86, 1.07)	**0.88 (0.79, 0.98)**	severity
	3856‡	1.07 (0.96, 1.20)	1.03 (0.92, 1.14)	severity
Aspirin administration ≤48 hours (Queensland hospitals)	4400	**0.91 (0.85, 0.98)**	0.94 (0.87, 1.02)	age, severity

* using multilevel modelling allowing hospital clustering
† among eligible patients
‡ among those with admission time ≤3.5 hours

Table 8-4. Mortality rate ratio up to 1 year after stroke for women compared to men with unadjusted and multivariable adjusted analyses

	N	Unadjusted MRR (95% CI)	Adjusted MRR* (95% CI)
All hospitals			
At 7 days	13304	**1.42 (1.25-1.60)**	1.09 (0.96-1.24)
At 30 days	13304	**1.45 (1.33, 1.59)**	1.07 (0.97, 1.17)
At 1 year, **without interaction** with severity	13304	**1.44 (1.34, 1.54)**	1.03 (0.95, 1.10)
At 1 year, unable to walk	8624	**1.36 (1.26, 1.47)**	1.05 (0.97, 1.14)
At 1 year, able to walk	4680	0.99 (0.80, 1.22)	0.81 (0.65, 1.00)
Queensland data			
At 7 days	4803	**1.22 (0.99, 1.50)**	0.93 (0.75, 1.16)
At 30 days	4803	**1.26 (1.09, 1.47)**	0.89 (0.76, 1.03)
At 30 days, ischemic stroke	3536	**1.45 (1.19, 1.76)**	0.87 (0.72, 1.07)†
At 1 year	4803	**1.32 (1.17, 1.49)**	0.90 (0.79, 1.01)
At 1 year, ischemic stroke	3536	**1.50 (1.24, 1.82)**	0.92 (0.75, 1.12)†

MRR: mortality rate ratio; CI: confidence interval

* adjusted estimates for age and severity of stroke

† adjusted estimates for age, severity of stroke, and aspirin ≤48 hours

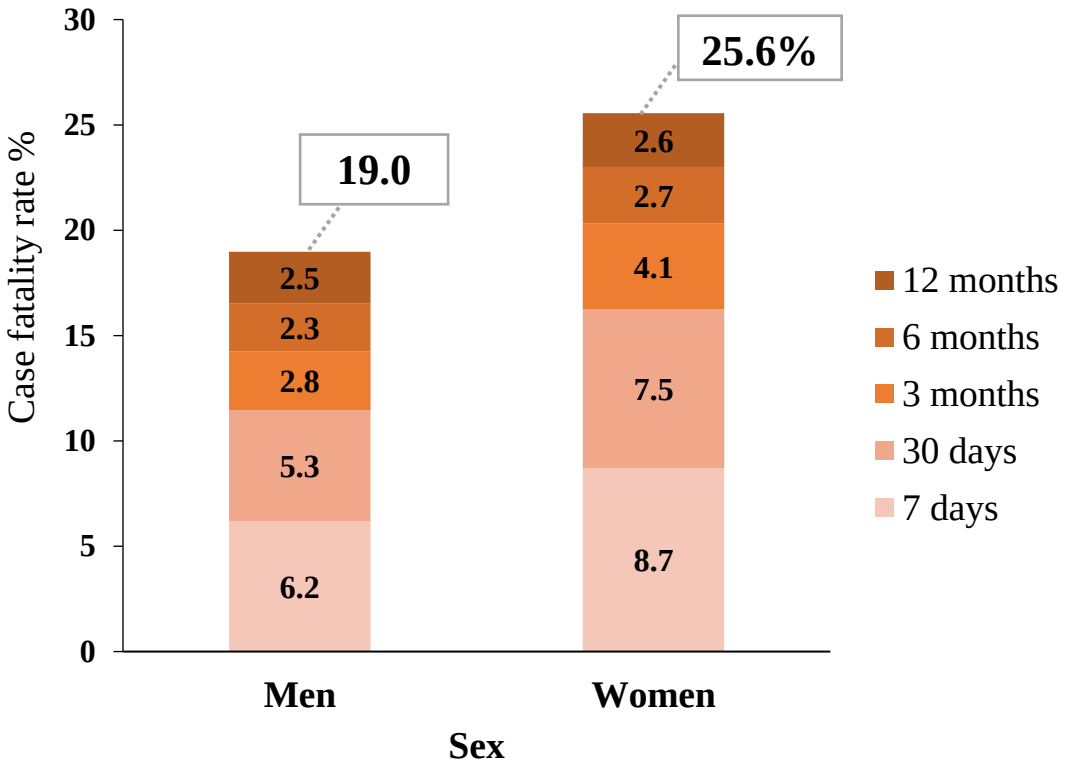


Figure 8-1. Case fatality rate up to one year after stroke among women and men with stroke in AuSCR (all hospitals)

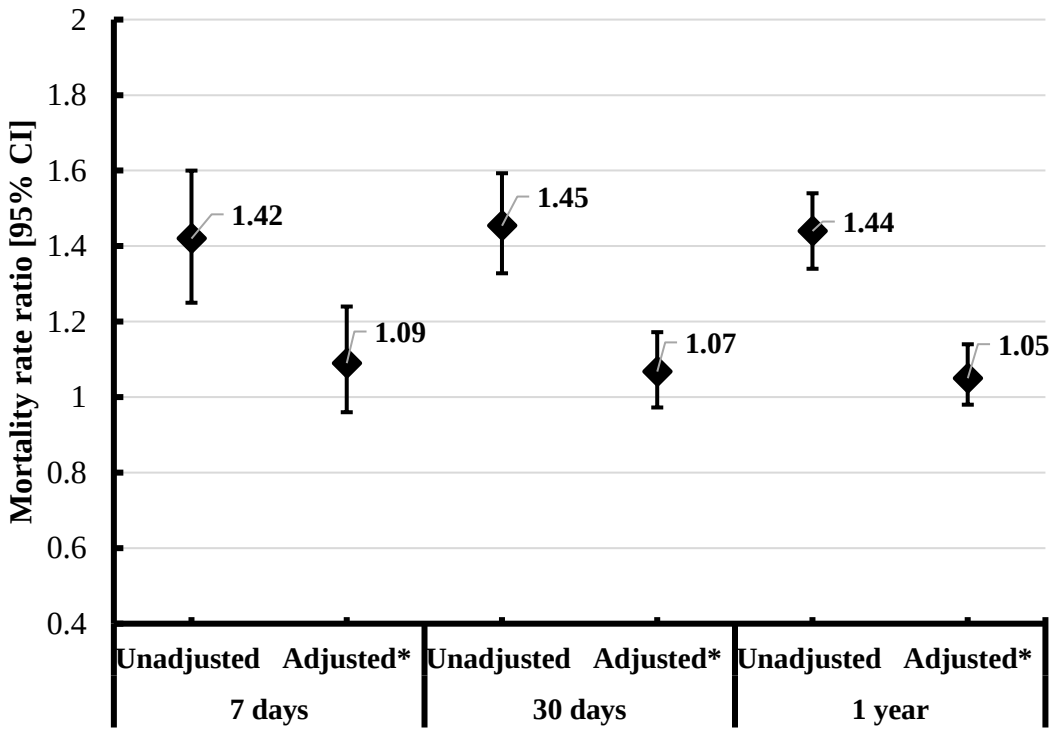


Figure 8-2. Mortality rate ratio for women compared to men (39 hospitals, n=13,304) at 7, 30 days, and 1 year after stroke. *adjusted for age and stroke severity (severe = unable to walk independently at admission; not severe = able to walk independently at admission)

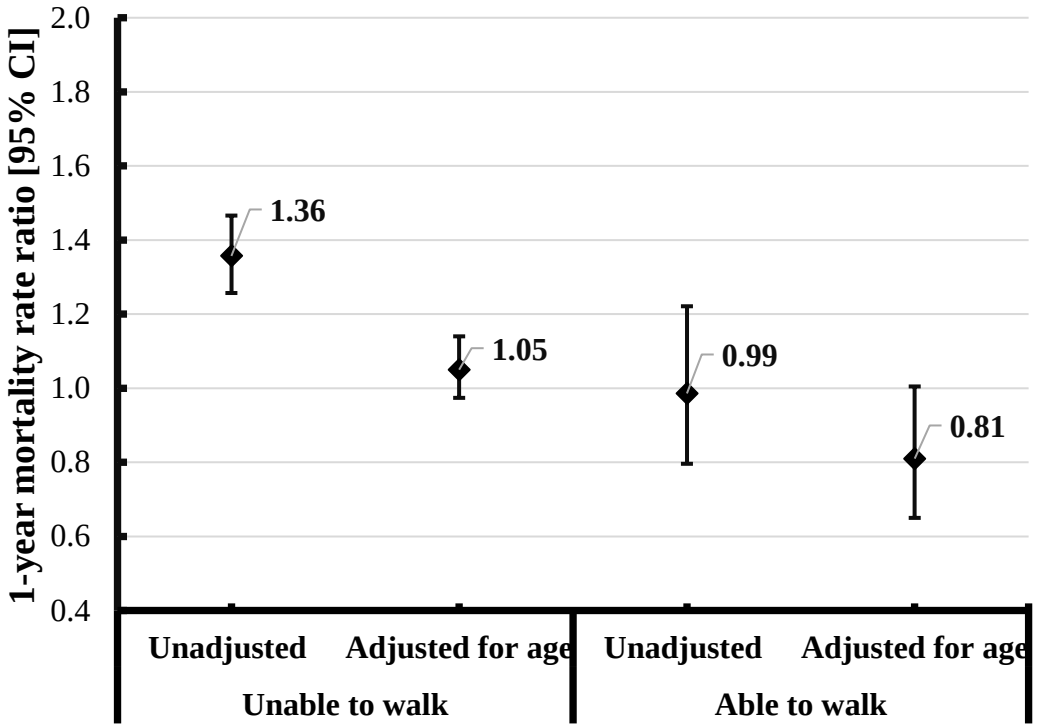


Figure 8-3. Mortality rate ratio for women compared to men (39 hospitals, n=13,304) at 1 year after stroke.

8.7 Supplemental Materials

8.7.1 Supplemental Methods

Statistical analyses

Variables were entered into the model only if they met all three criteria that defined them as confounders:[207] (1) the covariate was associated with the outcomes, $P<0.1$; (2) the covariate was associated with sex, $P<0.1$; and (3) the inclusion of the covariate changed the magnitude of the coefficient for the sex difference in the outcome ([unadjusted β-adjusted β]/unadjusted β*100%) by ≥10%.

Analyses of stroke unit access, receiving comprehensive discharge care plan if discharged to the community (i.e. to a home or aged care), being discharged on antihypertensive agents, mobilisation during admission (Queensland only) and speech pathologist review (Queensland only) were undertaken among all hospitalised patients irrespective of stroke type. However, analyses of intravenous thrombolysis, aspirin administration (Queensland only) and being discharged on antiplatelets or antithrombotics (Queensland) were performed only for those with confirmed ischaemic stroke.

Then, in the relevant subgroups specified above, we examined whether any factors related to processes of care that showed a sex difference were confounders of the association between sex and mortality. Some medication restrictions may be appropriate given patient's contraindication or to meet treatment guidelines.[319]

8.7.2 Supplemental Results

In sensitivity analysis of multiple imputation to account for missing data of confounders, estimates from imputed analysis were similar to the complete-case analysis in both at 30 days and 1 year after stroke (**Appendix E: Supplemental Table E-3**). In analyses of the role of early deaths (**Supplemental Table E-4**), excluding deaths ≤7 days produced almost no change in the magnitude of sex differences in mortality at 30 days. In 1-year analyses, however, the greater mortality was substantially driven by early deaths occurring within the first 6 months after stroke and the mortality rate in both sexes became more equal during the period of 6 months to 1 year after stroke.

The data from Queensland accounted for 37% of the whole registry. We have identified that the magnitudes of sex difference in mortality of stroke after stroke in Queensland hospitals, compared to the whole cohort, were smaller (30-day $MRR_{unadjusted}$ 1.45 vs 1.26; 1-year $MRR_{unadjusted}$ 1.44 vs 1.32); but, the contributing

factors to the differences were the same across regions including age and stroke severity.

The proportions of females between Queensland and non-Queensland patients with stroke were similar (**Supplemental Table E-5**). Although patients with stroke in Queensland, compared to non-Queensland patients, were slightly younger, less able to walk on admission, more often in disadvantaged socioeconomic groups and less often given evidence-based therapies, these differences were not statistically significant. There was a significant difference in intravenous thrombolysis administration in Queensland (8.8%) compared to elsewhere (14.4%; **Supplemental Table E-5**). A greater proportion of hospitals in Queensland (36.5%) were in regional areas compared to other states (Victoria: 11.7%, New South Wales: 21.6%, Western Australia: 0%)

8.7.3 Co-investigators and other contributors

Co-investigators and other contributors to the Australian Stroke Clinical Registry 2010-2014

The following people are acknowledged for their contribution in the Australian Stroke Clinical Registry (AuSCR) including participation on governance committees or contributions to data collection. The following does not include co-authors on this paper who may have one or more of the roles outlined below.

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Chapter 9: Sex differences in specific-cause mortality and excess death rates after stroke: the Australian Stroke Clinical Registry

9.1 Preface

At the time of submission of this thesis, the contents of this chapter have been circulated to co-authors in preparation for submission for publication.

Phan HT, Gall SL, Blizzard CL, Lannin N, Thrift AG, Anderson CS, Kim J, Grimley R, Castley HC, Hand P, Cadilhac D. Sex differences in specific-cause mortality and excess death rates after stroke: the Australian Stroke Clinical Registry.

9.2 Abstract

Background: Uncertainty exists over the sex differences in causes of death (COD) and specific-cause of excess mortality after stroke.

Methods: First-ever strokes (2010-2013) admitted to 35 hospitals participating in the Australian Stroke Clinical Registry were linked to national death registrations. One-year COD were categorised as stroke, ischaemic heart disease (IHD), other cardiovascular disease (CVD) e.g. hypertension, cancer, and other. Competing risk models were used to estimate female:male specific hazard ratios (sHRs) of death with adjustment for factors that differed by sex (sociodemographics, stroke severity). Age-

and sex-specific death rates by calendar year expected in the general population were derived from national data. Female:male standardised mortality ratio (SMR; observed/expected deaths) were estimated for COD.

Results: Among 9,441 admissions (46% women), women were 7 years older than men, had more severe strokes, received similar acute care therapies, and had greater all-cause mortality (25.4% vs men 19.1%, p<0.001). Women had greater risk of death associated with stroke ($sHR_{unadjusted}$ 1.65, 95% CI 1.42-1.91) and other CVD ($sHR_{unadjusted}$ 1.65, 95% CI 1.29-2.12), but these differences were explained by age

and stroke severity (stroke: $sHR_{adjusted}$ 1.19, 95% CI 1.02-1.40; other CVD: $sHR_{adjusted}$ 1.12, 95% CI 0.85-1.48). Compared to population norms, those surviving to 30-days had an >8-fold increased risk of death from stroke/recurrent events ≤1 year irrespective of sex (SMR: women 8.8; men 8.3). The excess risk of death from other CVD was greater in women than men (SMR 3.6 vs 2.8; p=0.26). Compared to population norms, the excess mortality after stroke was greater for IHD (SMR: women 3.0; men 3.5,) and cancer (SMR: women 2.6; men 2.6).

Conclusion: COD after first stroke differ between sexes with women having more deaths attributed to stroke or other CVD, which were mostly explained by age and stroke severity. Secondary stroke prevention should target vascular risk factors and co-morbidity.

9.3 **Introduction**

Women have been reported to have greater all-cause mortality in the long term after stroke than men. We have previously reported that women have greater all-cause mortality compared to men at 1 and 5 years in unadjusted analyses, but that this is mostly associated with deaths in the first 6 months.[236] It may be that there are discrepancies between men and women in their causes of death (COD) after stroke that potentially vary over time.

In the studies of COD up to 10 years after stroke, the authors have failed to report sex-specific findings[347] or investigate the factors contributing to differences in COD between men and women.[230,348,349] The association between sex and COD has mostly been reported as an incidental finding in multivariable models (e.g. using step-wise regression).[348,349] The current research is also limited by the fact that most of the data were collected in the 1970s and early 1990s when neuroimaging (e.g. CT scan) was irregularly used.[348,349] Lack of imaging information may influence the diagnosis and determination of underlying COD after stroke. Further, there is some evidence that women receive evidence-based care less often than men.[80,84] It is uncertain whether such differences in stroke care contribute to the sex differences in cause-specific mortality after stroke.

Furthermore, little is known about attributable causes for excess mortality after stroke compared to the general population, including any differences by sex. Hansen and colleagues (2001)[230] reported that the excess 1-year mortality post-stroke due to cardiovascular diseases, cancer, or other conditions compared to the general

population were greater in women than men. However, this research was conducted from 1982-1991 and may not represent the contemporary impact of stroke.

The aims of this study were to (1) examine whether the COD up to 1 year after stroke vary by sex and over time among people admitted to hospital with acute stroke in Australia, (2) identify the factors, including access to evidence-based care, that may account for any sex differences in COD, and (3) calculate the excess mortality atributable to stroke and other causes compared to the general population.

9.4 **Methods**

The data for this study was obtained from the Australian Stroke Clinical Registry (AuSCR) which is a national registry on the quality of acute stroke care and patient outcomes in Australia.[236] As a nationwide, multicentre, prospective registry, the AuSCR incorporates standardised methods of data collection using a validated system.[317]

Our research proposal was approved by the AuSCR Research Task Group and its Management Committee in August 2016 to examine sex differences in hospital processes of acute care and patient outcomes up to 1 year after stroke using the 2010-2014 AuSCR dataset. Appropriate ethics and/or governance approvals were obtained for all participating hospitals in AuSCR and the Australian Institute of Health and Welfare to conduct data linkage to national death registrations, known as the National Death Index (NDI). This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0015287).

Due to the lag times for receiving COD as part of updating the NDI,[350] only a subset of strokes enrolled in the AuSCR database between 2010 and 2013 (n=35 hospitals) were linked with COD for the analysis.

9.4.1 Study factors

Factors used on covariates in the analysis included patient characteristics and specific care processes received in the hospital that might explain the sex differences in COD after stroke. These predictors were categorised into five groups including: (1) socio-demographics, (2) stroke-related factors (e.g. stroke severity, stroke type, and cause of stroke known defined according to the TOAST criteria),[351] (3) processes of care provided in the hospital such as access to stroke units, (4) discharge information (length of hospital stay, discharge destination), and (5) 90-180 day post-stroke factors (e.g. living arrangements, self-reported recurrent stroke event, and readmission since discharge).

Sociodemographic factors included *age, country of birth, ethnicity, state of residence* (New South Wales, Queensland, Western Australia, Victoria, and Tasmania), and *socioeconomic position* determined using the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) using patient postcodes.[322] The IRSAD information was presented as predetermined quintiles with a higher quintile indicating greater socioeconomic advantage.

The ability to walk independently on admission was used as a proxy assessment of stroke severity.[236,328] This indicator has been proven as a reliable predictor of stroke

severity in the absence of a neurological scale such as the National Institute Health Stroke Scale.[323] Stroke type was categorised into three groups including *ischaemic stroke, intracerebral haemorrhage* and *undetermined stroke*. Information on the time from stroke onset to hospital arrival, and whether patients were transferred from another hospital were also collected.

The four processes of care collected for all patients (n=35 hospitals) included *access to stroke unit care, intravenous thrombolysis if an ischaemic stroke, care plan provided at discharge*, and being *discharged on antihypertensive agent(s)*.[319,324] Four additional processes of care were collected in the state of Queensland (n=21 hospitals) including: *mobilisation during admission, swallow screen, aspirin administration ≤48 hours* (ischaemic stroke), and *being discharged on antiplatelets or antithrombotic medications* (ischaemic stroke).

The length of stay was counted as the date of discharge minus the date of admission. Discharge destination after acute phase of stroke was categorised into *home, residential aged care, inpatient rehabilitation, and other places*.

Eligible AuSCR participants were surveyed between 90 and 180 days after stroke to self-report their current residence (i.e. *aged care, home, rehabilitation centres, and other)* and living arrangements *(whether the registrant lives alone)*. The presence or absence of a recurrent stroke event and readmission since discharge from the hospital (i.e. *readmission date and reasons*) were also self-reported by the registrants or their next-of-kin/key contact person.

9.4.2 Outcome measurements

Survival and COD up to 1 year after stroke were obtained from patient-level data linkage to national death registrations undertaken by the Australian Institute of Health and Welfare (AIHW). The records of deaths registered in Australia were certified by a medical practitioner on a Medical Certificate of Cause of Death or by a coroner.[350] The accuracy of the COD is ensured by working with providers, quality checks during the data process and training of staff.[350] The COD were based on ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) codes. The primary COD were classified into: stroke, ischaemic heart disease − IHD, other cardiovascular disease – CVD (e.g. *hypertension, atrial fibrillation, heart failure, peripheral vascular diseases, and others*), cancer, other causes (*other diseases, accidents, unclassified conditions*), and unknown cause (*missing ICD-10 codes on death records*).

9.4.3 Statistical analysis

Statistical analyses were performed using Stata 12.1 (StataCorp Texas, 2011).[269] All two-tailed p-values ≤0.05 were considered statistically significant.

Multilevel competing risk modelling, accounting for the hospital as a unit of patient clusters, was used to estimate female:male specific hazard ratios (sHRs) of specific COD up to 1 year after stroke.

To assess the role of covariates on the association between sex and each outcome, we used purposeful model building.[207] Variables were entered into the model only if they

met all three criteria that defined them as potential confounders.[207] The model-building process was initially undertaken for each covariate separately and then confounding or contributing factors were included in the multivariable models (similar to those described earlier in **Supplemental Methods**: section **8.7.1)**. The modifying effect of time to death and other covariates on the sex difference was assessed by a test of the statistical significance of the coefficient of a sex × covariate product term.

Estimates of the sex differences in processes of care and mortality after stroke were performed for all hospitals (4 indicators) and in the Queensland subset of patients that had more detailed information on stroke care (4 additional indicators). In the relevant subgroups, we examined whether any factors related to processes of care that showed a sex difference were contributing factors to the association between sex and mortality (similar to those described earlier in **Supplemental Methods**: section **8.7.1**).

Stroke severity indicated by the walking ability on admission has been proven as a predictor of all-cause mortality and contributing factor to the greater mortality in women after 1 year after stroke using the same dataset (**Chapter 8**). We hypothesised that stroke severity would also be associated with specific COD following stroke, and examined the role of stroke severity on the association between sex and each COD.

Comparison of patients with stroke and the general population

For this analysis, 1-year COD due to stroke, ischaemic heart disease (IHD), other vascular conditions (e.g. hypertension), and cancer were investigated. Age and sex

specific death rates for each COD by calendar year expected in the general population were derived from Australian data (Stroke and other CVD: Australian heart disease statistics 2016 by the National Heart Foundation;[352] cancer: data published by the AIHW).[353]

Expected deaths were estimated for each sex by multiplying the age-specific person-years of observation in the study group (stroke registrants) by the death rate of the general population, and summing the values for each age group to calculate the number of expected deaths. We then estimated the standardised mortality ratio (SMR) which was the quotient of the observed to the expected numbers of deaths for each COD, separately for women and men. The absolute excess risk (AER) for each COD was also estimated to compare the absolute additional mortality between men and women at 1 year after stroke (AER= [expected – observed deaths]/age-specific person-years at risk ×100). Noting that stroke-specific mortality is largely driven by 30-day deaths, we reported the 1-year SMR and 1-year AER due to stroke among those deceased after 30 days (often called non-fatal strokes[230]).

9.5 **Results**

There were 9,441 patients experiencing first-ever stroke between 2010 and 2013 with 81% ischaemic, and 46.4% being female. Median age of stroke was 75 years (Interquartile range 64-84).

Sex differences in patient characteristics

Based on socio-demographic and stroke-related characteristics (**Table 9-1**), women were about 7 years older than men (median age 78.8 vs 72.0, p<0.001) and were less likely to walk independently at time of admission (indicating more severe strokes; 38.5% vs 55.6%, p<0.001).

Women had fewer known causes of stroke and experienced more stroke events while in hospital for another condition (in-hospital stroke) compared to men. We found that men and women received similar acute care (**Table 9-1**) except that women were less often administered aspirin ≤48 hours than men (49.6% vs 60.2%, p=0.042) based on the subset of Queensland data (n=21 hospitals; n=2,972), regardless of whether or not early deaths ≤48 hours were excluded. When compared to men, women were more often discharged to aged care (7.7% vs men 3.4%; p<0.001), and less often discharged directly home from acute care (33.9% vs men 42.5%; p<0.001, **Table 9-2**). At 90-180 days after stroke, women were more likely to live alone (25.8% vs men 16.7%, p<0.001) and less likely to stay at home (87.5% vs men 77.9%).

Sex difference in specific COD after stroke

Women had greater all-cause mortality (25.4% vs men 19.1%, p<0.001) at 1 year after a first-ever stroke. Stroke and CVD (i.e. IHD and other cardiovascular conditions) were the most common COD, accounting for over half of deaths 1 year following stroke. However, the distribution of COD differed between the sexes. Among those deceased by any cause (n=2,080; **Figure 9-1**), men had more deaths due to cancer (13% vs women 6%) and IHD (8% vs women 6%) while women had more deaths attributed to stroke (50% vs men 41%) or other CVD (16% vs men 13%). The

proportion of missing ICD codes for COD was relatively equal between sexes (women 9%; men 10%). Further details of the distribution of COD for women and men by age group and time to death are provided in the **Appendix F**: **Supplemental Figures F-1** and **F-2**.

For other CVD mortality at 1 year after stroke, women more often died from atrial fibrillation (49.2% vs 45.0%) and heart failure (5.5% vs 3.1%) than men. Among those who died due to cancer, more men than women died from urinary tract cancer (7.5% vs 2.9%) or skin cancer (9.2 vs 5.7%), while more women than men died from lung (18.6% vs 11.7%) or digestive system (32.9% vs 25.8%; **Supplemental Table F-1**) cancers.

Sex difference in specific-cause mortality after stroke

Data were available for 94% (n=8,889) of the 9,411 patients because of missing data on covariates including age and stroke severity. Women were 39% more likely to die by 1 year after stroke compared to men in unadjusted analysis (female:male hazard ratio, HR 1.39, 95% CI 1.23-1.56). Advanced age and more severe strokes in women, compared to men, explained their greater all-cause mortality ($HR_{adjusted}$ 1.01, 95% CI 0.89-1.15).

In specific-cause mortality 1 year following stroke, more severe stroke, indicated by being unable to walk independently on admission, was associated with increased risk of death in all COD groups except cancer (**Supplemental Table F-2**). Women had a 65% greater risk of death associated with stroke than men ($sHR_{unadjusted}$ 1.65, 95% CI

1.42-1.91; **Table 9-2**). The sex difference was greatly attenuated after adjusting for age and stroke severity ($sHR_{adjusted}$ 1.19, 95% CI 1.02-1.40).

Women appeared to face a lesser risk of death due to IHD ($sHR_{unadjusted}$ 0.88, 95% CI 0.65-1.18; $sHR_{adjusted}$ 0.58, 95% CI 0.43-0.77), but they more often died from other CVD i.e. atrial fibrillation and heart failure ($sHR_{unadjusted}$ 1.65, 95% CI 1.29-2.12). The greater risk of death due to other CVD in women was similarly accounted for by age and stroke severity ($sHR_{adjusted}$ 1.12, 95% CI 0.85-1.48).

The risk of death attributable to cancer was less in women ($sHR_{unadjusted}$ 0.69, 95% CI 0.50, 0.95) than in men and the sex difference remained significant after accounting for age ($sHR_{age\text{-}adjusted}$ 0.67, 95% CI 0.50-0.91). None of the factors including stroke type (**Supplemental Figure F-3**), time to death (**Supplemental Table F-3**), four indicators of processes of care available among all hospitals, and other covariates confounded or modified the sex difference in cause-specific mortality up to 1 year after stroke.

In the subset of the Queensland patients, women also had greater all-cause ($HR_{unadjusted}$ 1.41, 95% CI 1.19-1.66) and stroke-specific mortality ($sHR_{unadjusted}$ 1.79, 95% CI 1.29-2.12) than men. Age, stroke severity and likelihood of early aspirin administration fully accounted for these sex differences (all-cause $HR_{adjusted}$ 0.92, 95% CI 0.80-1.05; stroke-specific $sHR_{adjusted}$ 1.04, 95% CI 0.76-1.42).

Sex difference in excess death rates after stroke

Compared to the general Australian population, patients with a first-ever stroke surviving to 30-days had an over 8-fold increased risk of death (standardised for age) due to the index stroke or a recurrent stroke within 1 year after stroke, irrespective of sex (SMR, Women: 8.8; Men: 8.3; p=0.656). The AER for stroke was 35.0/1,000 person-years in women and 17.4/1,000 person-years for men (**Table 9-3**; p<0.001). People with stroke were also more likely to die from IHD within 1 year than the general population, but the excess mortality, standardised for age, was slightly greater in men (SMR men 3.5 vs 3.0; p=0.310). By contrast, the excess risk of death from other CVDs among those with stroke, compared to the general population, was greater among women than men (SMR women 3.6 vs 2.8; p=0.026). Men and women with stroke shared an equal 2.6-times greater risk of death caused by cancer than expected although the number of cancer deaths was small (**Table 9-3**).

9.6 **Discussion**

In this paper we provide contemporary data on the sex differences related to COD after stroke and the excess risk of death compared with the general population. We found that the mortality up to 1 year after stroke was mostly associated with cardiovascular diseases and cancer, and the COD differed by sexes. Women had more deaths due to stroke and other CVDs (not including IHD) while men had greater risks of death by IHD or by cancer. Women's advanced age and more severe strokes (indicated by the inability to walk independently at admission) were attributed to the increased risk of death due to stroke and other CVD (i.e. atrial fibrillation, heart failure). In a subset of the cohort, women were less often treated with aspirin ≤48

hours of an ischaemic stroke and this explained part of the sex difference in stroke-specific mortality. None of the other evidence-based therapies contributed to the sex differences in specific-cause mortality after stroke.

In the first year following stroke, both men and women surviving to 30 days had at least 8 times excess mortality from stroke compared to people of the same age and sex in the general population. Patients that had been hospitalised with stroke, regardless of sex, were 3 times more likely to die from other CVD and 2.6 times more likely to die from cancer than the general population. These findings are in line with research by Brønnum-Hansen et al.[230]

More deaths due to stroke in women

Age was the most important factor contributing to 51% of the sex differences in stroke-specific mortality. Older age can reflect the multimorbidity[15] and underreceipt of evidence-based stroke care[214] which are associated with lower survival after stroke. It is critical to develop clinical recommendations that incorporate age-related complexities (e.g. multimorbidities and polypharmacy) as these may optimise the outcomes of older patients with stroke.

Stroke severity accounted for 24% greater stroke mortality in women compared to men, supported by the current evidence.[236] Targeting modifiable factors contributing to stroke severity, e.g. hypertension,[244] and AF[245], could lessen the sex differences. The ability to walk on admission, as a proxy for stroke severity,[323] appeared to be a reliable predictor of mortality outcome in the study. The collection of NIHSS data in

AuSCR was introduced in 2015, and in the future may allow more opportunities to explore why women have more severe strokes than men.

The receipt of aspirin administration contributed to the sex difference in stroke mortality but the data were only available in a subset of Queensland hospitals. The undertreatment with antiplatelet or anticoagulants in women has been observed previously,[334] suggesting a need to ensure greater access to early treatment with aspirin for women. Although the sex difference in aspirin administration was not fully explained by the covariates collected in the AuSCR, other unmeasured factors, such as complications and contraindications to treatment (e.g. allergy, bleeding disorder, or uncontrolled hypertension),[336] may play a role. Since mid-2016, there has been an expansion to the whole registry on data collection of additional processes of care measures (i.e. aspirin administration) and contraindications are noted for some of these. A sex bias in the early treatment of aspirin may warrant further examination to inform clinical practice and provide more opportunities to address the sex differences in mortality after stroke.

The role of stroke severity in mortality due to CVD

We found that the walking ability on admission, as a proxy for stroke severity,[323] was associated with increased risk of death due to IHD and other CVD, and this covariate also contributed to their greater cause-specific mortality in women. The finding is in line with evidence that a slow walking speed in older people is strongly linked to greater CVD mortality.[354] Although uncertainty exists over the causal pathway of the association between stroke severity and increased risk of dying from CVD, there are

some potential explanations. Inability to walk on admission could reflect the presence of functional limitation before stroke that is associated with chronic diseases including cardiovascular conditions.[236,265] Although early mobilisation is recommended in clinical guidelines[324,355] to improve walking and functional independence,[356] only 40% of patients were mobilised ≤48 hours in our study (**Table 9-2**). This suggests another possibility that restricted mobility caused by stroke (i.e. hemiplegia, paraplegia), indicated by walking ability on admission, may persist into the longer term following stroke. Those people with restricted mobility (pre-existing or following stroke) may face a high risk of venous thromboembolism and cardiovascular events,[357] potentially leading to greater CVD mortality.[358]

More deaths due to other CVD in women

Women with stroke, compared to men, were at higher risk of death due to other CVD (not including IHD), particularly atrial fibrillation (AF) and heart failure, and the difference was accounted for by age and stroke severity. This finding was consistent with the sex differences in the comorbidity profile of those with stroke with women being older, frailer and with more AF and more hypertension compared to men.[236] The suboptimal management of AF such as undertreatment with anti-coagulants among older patients,[225] many of whom are women, underpins the need for better detection and treatment of AF in older men and women.

Fewer deaths due to IHD or cancer in women

Men with stroke had an increased risk of death from IHD than women and adjustment for age and stroke severity underpinned the association. This can be explained because men appear to develop IHD and stroke at a younger age and have less severe strokes compared to women. Those men with stroke are also presented with worse lifestyle risk factors (e.g. smoking, alcohol consumption) or medical histories (i.e. more often having a history of coronary heart disease) that may lead to their higher IHD mortality.[236]

Men with stroke had a greater 1-year risk of death due to cancer than women although the number of cancer deaths were small. The finding is consistent with the evidence that men are at greater risk of cancer incidence and mortality compared to women.[359] The excess burden of cancer in men is possibly explained by multiple factors including their worse lifestyle risk factors, as mentioned above, and less help-seeking compared to women.[359]

Excess deaths due to stroke, CVD, and cancer for both men and women

People with stroke had excess deaths due to stroke, other CVD, and cancer when compared to the general population. This could be explained by the fact that these causes of death share common risk factors, such as hyperlipidemia, diabetes, and smoking.[360] The excess mortality due to stroke and CVD could also be related to a common mechanism (atherosclerosis) of these diseases.[361] Prevention strategies should be prioritised by targeting vascular risk factors and co-morbidities to improve survival following stroke. At the patient level, some potential programs based on fitness training alone or in combination with psychosocial or educational

interventions may have some benefits on preventing stroke, like the exercise-based cardiac rehabilitation has had, particularly on reducing CVD mortality.[362,363] Population-based prevention strategies could offer an excellent option to improve outcomes after stroke. For example, the use of 'polypill' therapy that combines multiple drugs (i.e. statin, antihypertensive agents, aspirin) could reduce stroke and other CVDs by 80% among those ≥55 years with existing CVD.[364] Moreover, it is essential to ensure access to evidence-based care for both men and women who experience stroke to promote a better chance of survival.[236]

There are two potential mechanisms for the excess death due to cancer among those with stroke. Cancer generally has a long development period, suggesting that deaths from cancer after stroke were mostly from pre-existing diseases. There is some discussion on screening for cancer in the patient with cryptogenic stroke that may help to diagnose occult cancer and inform future interventions, but the cost-effectiveness of this approach warrants more research.[365,366] The other potential mechanism is related to newly diagnosed cancer patients who have a stroke possibly due to hypercoagulation (i.e. causing thromboembolism)[367] or side-effects of cancer treatment.[368] Given the lack of cancer-related data in stroke studies, it may be useful to further examine the predictors of long-term outcomes among people with stroke and cancer, potentially using data linkage. Because patients with stroke and a history of cancer have an increased risk of recurrent stroke and cardiovascular mortality,[365] these outcomes should be considered in future stroke research together with other data including cancer treatment (e.g. chemotherapy, radiotherapy). Understanding the

interrelationships between cancer and stroke is important given the large burden associated with these two diseases.[368]

Strengths and limitations

To our knowledge, this is the first study using a national stroke registry to examine sex differences in cause-specific mortality 1 year after stroke. Our research also provides the excess death rate according to each COD after stroke (i.e. stroke, IHD, other CVD, and cancer) for both men and women compared to the Australian general population. The findings were based on a large high-quality dataset, enabling us to have enough reliability and power to test our hypotheses. Stroke performance indicators in the AuSCR were aligned with high priority national clinical recommendations, making our work relevant to current clinical practice. The AuSCR data on survival and COD linked to the national registration minimised selection bias from missing death records (only 10% of registrants had unknown COD).

We acknowledge some limitations of the study. Some potential confounding factors of the sex differences in mortality after stroke, including living arrangement before stroke, behavioural risk factors, pre-stroke function, comorbidities, and other processes of care were unavailable. However, in our earlier work using data from 13 population-based studies,[236] there were very few differences between men and women in the treatment and management of stroke (i.e. brain imaging, cardiac workup, admission and discharge medications). The AuSCR sample was consistent with other representative stroke populations.[236] For example, the all-cause mortality by 1 year (22%) was comparable to other similar studies worldwide.[236] However, patients

registered in the AuSCR hospitals during the study period were mainly admitted to neurology/stroke units and from metropolitan areas.[236] The possibility of bias caused by this cannot be eliminated, which is another limitation of the study.

Conclusion

In this study, we found that women, compared to men, more often died at 1 year after stroke and the COD varied by sexes. Women had more deaths attributed to stroke or other CVD than men, and the difference was mostly accounted for by their advanced age and stroke severity. Women's lesser receipt of aspirin therapy also contributed to their increased risk of stroke-specific mortality. Compared with the general population, excess mortality for both men and women was mostly attributed to stroke or recurrent events, other cardiovascular conditions, and cancer. Our findings reinforce the need for better prevention of stroke and CVD in men and women. It is also necessary to deliver high-quality stroke care to all people that suffer stroke as this is associated with better survival and other outcomes.

Table 9-1. Characteristic of AuSCR registrants for first−ever stroke during 2010−2013 (n=35 hospitals) by sex

	Men	Women	p−value
	n (%)	n (%)	
Number of cases	5059 (53.6%)	4328 (46.4%)	<**0.001**
Sociodemographics			
Age, median (IQR)	72.0 (61.8−81.0)	78.8 (67.8−85.9)	<**0.001**
State			
New South Wales	1360 (26.9%)	1067 (24.4%)	0.221
Queensland	1574 (31.1%)	1398 (31.9%)	
Tasmania	216 (4.3%)	193 (4.4%)	
Victoria	1651 (32.6%)	1535 (35.0%)	
Western Australia	258 (5.1%)	189 (4.3%)	
Born in Australia	3224 (63.7 %)	2939 (67.1%)	0.066
Aboriginal/Torres Strait Islander	55 (1.1%)	57 (1.3%)	0.168
Socioeconomic status			
IRSAD1 (most disadvantage)	988 (19.5%)	783 (17.9%)	0.635
IRSAD2	871 (17.2%)	752 (17.2%)	
IRSAD3	840 (16.6%)	705 (16.1%)	
IRSAD4	936 (18.5%)	840 (19.2%)	
IRSAD5 (least disadvantage)	1424 (28.2%)	1302 (29.7%)	
Stroke−related factors			
Transfer from other hospital	791 (15.6%)	616 (14.1%)	0.100
In−hospital stroke	264 (5.2%)	278 (6.3%)	**0.020**
Time (minutes) from onset to arrival, median (IQR)	181 (78−679)	170 (78−596)	0.983
Walking independently at admission (proxy for less severe stroke)	1949 (38.5%)	2812 (55.6%)	<**0.001**
Cause of stroke known	2415 (47.7%)	1993 (45.5%)	**0.001**
Type of stroke			
Intracerebral haemorrhagic (ICH)	826 (16.3%)	744 (17.0%)	0.724
Ischaemic stroke	4071 (80.5%)	3490 (79.6%)	
Undetermined	159 (3.1%)	148 (4.4%)	
Processes of care received in hospital			
Treated in stroke units	4103 (81.1%)	3434 (78.4%)	0.258
Intravenous thrombolysis*	519 (12.8%)	418 (12.1%)	0.298
Discharged on antihypertensives†	3133 (69.5%)	2568 (68.9%)	0.634
Care plan for discharge to the community‡	1138 (49.0%)	866 (47.5%)	0.487
Discharge information			
Discharge destination			
Home	2150 (42.5%)	1486 (33.9%)	<**0.001**
Inpatient rehabilitation	1510 (29.9%)	1339 (30.6%)	

	Men	Women	p−value
	n (%)	n (%)	
Residential aged-care facility	174 (3.4%)	337 (7.7%)	
Other hospitals/facilities	764 (15.1%)	668 (15.2%)	
Died in hospital	461 (9.1%)	552 (12.6%)	
Length of stay (LOS), median (IQR) days†	6 (3−10)	6 (3−12)	1.000
Self-reported 90-180 day covariates			
Current residence†			
Aged care	201 (7.7%)	353 (17.1%)	**<0.001**
Home	2240 (85.3%)	1573 (76.1%)	
Rehabilitation	52 (2.0%)	25 (1.2%)	
Hospitals/other	132 (5.0%)	117 (5.7%)	
Recurrent stroke	106 (2.1%)	102 (2.3%)	0.443
Living alone	408 (8.1%)	538 (12.3%)	**<0.001**
Readmission	512 (10.1%)	389 (8.9%)	0.366
Additional processes of care in hospital (Queensland; 21 hospitals)			
Number of cases	1574 (53.0%)	1398 (47.0%)	**<0.001**
Mobilisation§	515 (59.1%)	454 (52.1%)	0.057
Mobilisation ≤48 hours§	383 (44.0%)	351 (40.3%)	0.764
Swallow assessment ≤24 hours	762 (48.4%)	604 (43.2%)	0.389
Aspirin administration ≤48 hours*	788 (60.2%)	570 (49.6%)	**0.042**
Discharged on antiplatelets/antithrombotics*†	755 (83.0%)	579 (79.6%)	0.666

IRSAD= the Index of Relative Socio-Economic Advantage and Disadvantage
* among ischaemic stroke
† among those discharged
‡ among those discharged to community (e, to a home setting or institutional residential aged care)
§ if unable to walk on admission

Table 9-2. Specific hazard ratio (sHR) of death up to 1 year after stroke for women compared to men in AuSCR 2010-2013 using competing risk models

Cause of death	**Unadjusted**	**Adjusted for**		
		Age	Stroke severity†	Age and severity
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
Stroke	**1.65 (1.42-1.91)**	**1.28 (1.10-1.49)**	**1.46 (1.25-1.71)**	**1.19 (1.02-1.40)**
Ischaemic heart disease	0.88 (0.65-1.18)	**0.60 (0.45-0.79)**	0.82 (0.60-1.12)	**0.58 (0.43-0.77)**
Other cardiovascular disease	**1.65 (1.29-2.12)**	1.19 (0.91-1.56)	**1.49 (1.16-1.93)**	1.12 (0.85-1.48)
Cancer	**0.69 (0.50-0.95)**	**0.67 (0.50-0.91)**	**0.69 (0.50-0.94)**	**0.67 (0.49-0.91)**
Other conditions	1.17 (0.87-0.58)	0.99 (0.70-1.36)	1.08 (0.79-1.47)	0.94 (0.68-1.30)
Unknown	1.12 (0.84-1.49)	0.89 (0.64-1.21)	1.05 (0.78-1.40)	0.86 (0.63-1.17)
All-cause	**1.39 (1.23-1.57)**	**1.08 (0.95-1.22)**	**1.26 (1.11-1.44)**	1.01 (0.89-1.16)

Bold denotes statistically significant results

† Walking ability independently on admission was used as a proxy for stroke severity (unable to walk=more severe; able to walk=less severe)

‡ the hazard ratio was estimated using Cox model

Table 9-3. Standardised mortality ratio (SMR) and absolute excess death rate (AER) among people with stroke compared to general population norms after age standardisation

	Men				Women			
Cause of death (COD)	Reference death rate*	Observed /Expected	SMR (95% CI)	AER (95% CI)†	Reference death rate*	Observed /Expected	SMR (95% CI)	AER (95% CI)†
Stroke, *died >30 days*	40.4	84/10.1	8.3 (6.7-10.3)	17.4 (13.2-21.6)	41.1	135/15.2	8.9 (7.5-10.5)	35.0 (28.3-41.7)
Stroke, *died ≤30 days*	NA	314/-	---	---	NA	425/-	---	---
Stroke, *all cases*	40.4	398/10.1	39.3 (35.6-43.4)	90.9 (81.7- 100.0)	41.1	560/15.3	36.5 (33.6-39.7)	158.3 (144.8-171.8)
Stroke, *not inc. recurrence‡*	40.4	396/9.8	40.2 (36.5-44.4)	92.7 (83.4-102.1)	41.1	553/14.8	37.3 (34.3-40.5)	160.9 (147.4-174.7)
Ischaemic heart disease	105.1	81/22.9	3.5 (2.8-4.4)	13.6 (9.5-17.7)	58.7	62/20.8	3.0 (2.3-3.8)	12.0 (7.5- 16.5)
Other CVD	197.2	129/46.3	2.8 (2.3-3.3)	19.4 (14.1-24.6)	143.4	181/50.4	3.6 (3.1-4.2)	38.0 (30.3-45.6)
Cancer	220.6	120/45.5	2.6 (2.2-3.2)	17.5 (12.4-22.5)	166.1	70/27.0	2.6 (2.1-3.3)	12.5 (7.7- 17.3)

Other CVD=Other cardiovascular disease (e.g. hypertension, atrial fibrillation, heart failure)

* death rate per 100,000 persons by each COD

† per 1,000 person-years

‡ self-reported recurrent event at 3 months after stroke (n=106 cases for men; 102 cases for women) was not included in the analysis

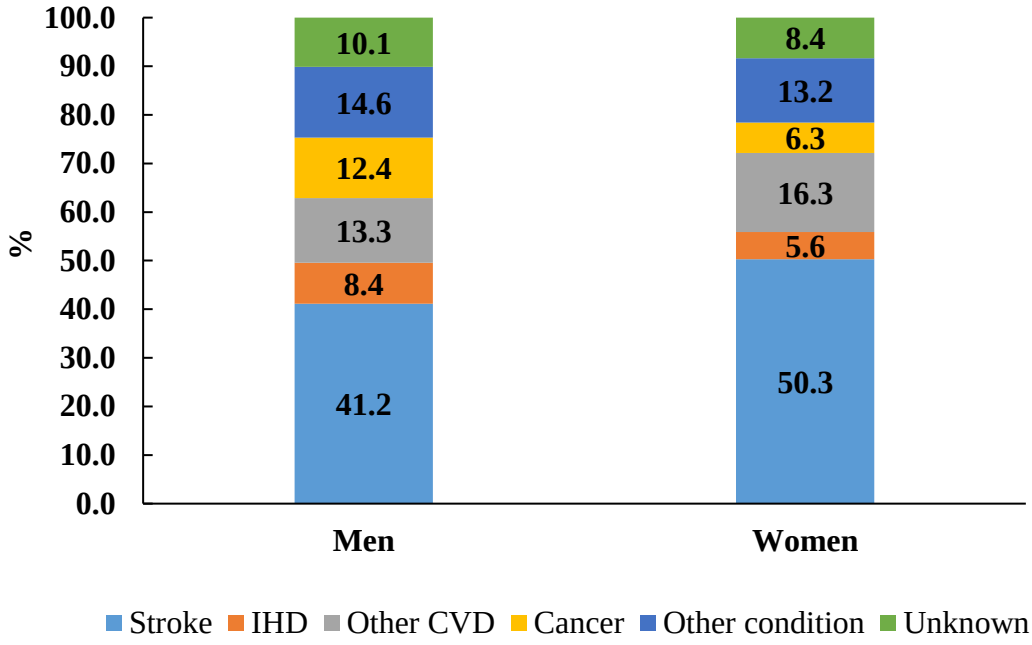


Figure 9-1. Causes of death up to 1 year after stroke by sex. (IHD=Ischaemic heart disease; CVD=Cardiovascular disease)

Chapter 10: Sex differences in health-related quality of life at 3-6 months after stroke: Australian Stroke Clinical Registry

10.1 Preface

At the time of submission of this thesis, the contents of this chapter have been circulated to co-authors in preparation for submission for publication.

Phan HT, Gall SL, Blizzard CL, Lannin N, Thrift AG, Anderson CS, Kim J, Grimley R, Castley HC, Hand P, Cadilhac D. Sex differences in health-related quality of life at 3-6 months after stroke: Australian Stroke Clinical Registry.

10.2 Abstract

Introduction: Women have worse health-related quality of life (HRQoL) after stroke than men but the reasons for this difference are uncertain.

Methods: We included first-ever strokes admitted to 39 hospitals participating in the Australian Stroke Clinical Registry (AuSCR; 2010-2014) with HRQoL assessed between 3-6 months after stroke using the European Quality of Life–5 Dimensions (EQ5D) instrument. Study factors included sociodemographics, stroke type, walking ability on admission (proxy for severity) and access to evidence-based care (e.g. stroke unit, intravenous thrombolysis, antihypertensive medications and discharge plan). EQ5D scores were calculated for each domain, and the results were then

transformed into a total utility value. Quantile regression modelling, unadjusted and adjusted for confounding factors, was used to calculate the median differences (MD) in EQ5D utility scores between women and men. Differences in utility scores within the range 0.08-0.12 unit were defined as clinically meaningful.

Results: About 60% (6852/11418) of survivors completed EQ5D assessment (median 139 days, interquartile range 123-161); 44% female. Women were older (median age 77.1 vs 71.2, p<0.001) and less able to walk on admission (37.9% vs 46.1%, p<0.001). Women had lower HRQoL compared to men in unadjusted analysis (MD -0.082 95% CI -0.099, -0.066). Age and stroke severity, but not clinical care, explained the sex differences whereby young men (aged <65 years) and older women (75^{+} years) had significantly poorer HRQoL after stroke.

Conclusion: Poorer HRQoL after stroke among younger men and older women were due to stroke severity and health differences in the population. Interventions to reduce the severity of stroke (e.g., managing risk factors, increasing access to care) for older patients should be prioritised to reduce the sex differences.

10.3 Introduction

Women have been reported to have poorer HRQoL after stroke than men; however, the factors that may explain sex differences in short- and long-term studies are poorly understood.[23,24] Many investigators did not report sex-specific outcomes.[170,173,369-373] Others have used prediction models that are not focused on the sex difference (e.g. using the step-wise approach) whereby sex was not retained in multivariable

models.[23,24] Another explanation may be related to the sex differences in stroke treatment since women often receive evidence-based care less often than men.[80,84] However, among a few studies specifically designed to examine the sex difference in HRQoL, the data on quality of care were lacking.[23] Therefore the impact of differences in clinical care between women and men on women's poorer HRQoL is inconclusive.

In our most recent meta-analysis of sex differences in HRQoL using individual participant data from four population-based studies conducted in Australasia and UK (Chapter 5), the greatest contributors to the worse HRQoL in women were advanced age, pre-stroke functional limitations, stroke severity, and the presence of long-term post-stroke mood disorders. Differences in stroke care did not account for the sex difference in HRQoL but the analyses were limited by the fact that the data on management were out of date. In study-specific analyses, there was some evidence that women still had worse HRQoL following stroke than men based on the fully-adjusted models. The sex differences may be further accounted for by unmeasured or poorly measured factors. Therefore, further research is required to investigate the reasons for the residual differences in HRQoL between men and women.

Additionally, while women appear to experience worse HRQoL after stroke than men, women without stroke also report poorer health status than men of all ages.[374] Therefore, it is uncertain whether the sex difference in HRQoL is caused by stroke or is due to other differences between men and women.

Our aims were to (1) quantify the sex differences in HRQoL between 3-6 months after stroke using contemporary data from the Australian Stroke Clinical Registry (AuSCR), (2) identify contributing factors, including processes of stroke care, which may contribute to the difference, and (3) compare the sex difference in HRQoL between those with and without stroke by using data from the AuSCR and population HRQoL norms derived from an Australian general population survey.

10.4 Methods

The Australian Stroke Clinical Registry (AuSCR) is a nation-wide prospective collection of data on stroke care.[236] Currently, more than 65 public hospitals around Australia contribute data to the AuSCR. The registry includes information on evidence-based therapies while in the hospital, outcomes and some patient characteristics. In this study, we included first-ever strokes admitted to 39 hospitals participating in the AuSCR database between 2010 and 2014.

10.4.1 Study factors

We examined a wide range of factors that might explain the sex differences including patient characteristics and in-hospital processes of care. The study factors collected from the AuSCR dataset were categorised into five groups. They included the following (1) socio-demographics: *age, country of birth, state of residential address* (New South Wales, Queensland, Western Australia, Victoria and Tasmania), and *socioeconomic position* determined using the Index of Relative Socio-Economic Advantage and Disadvantage;[322] (2) stroke-related factors: *stroke severity* (ability to

walk on admission), *stroke type* (ischaemic, intracerebral haemorrhage and undetermined stroke), *time from stroke onset to hospital arrival,* and *whether patients were transferred from another hospital*; (3) treatment and management (processes of care recommended in Australian clinical guidelines:[324,355] *stroke unit access, intravenous thrombolysis, use of antihypertensive agent(s) at discharge,* and *receipt of a discharge care plan*; (4) discharge information: *length of stay* and *discharge destination*; and (5) post-stroke factors (3-6 month status): *survival, recurrent stroke, whether the patient was living alone, HRQoL (see below)* and *proxy assessment by caregivers* (as required).

Four additional care processes were only collected in the state of Queensland (n=21 hospitals) including *mobilisation during admission, swallow screen, aspirin administration ≤48 hours,* and *being discharged on antiplatelet or antithrombotic medications* (ischaemic stroke).

10.4.2 Outcome measure

The collection of patient-reported outcomes occurred between 3-6 months after the index event using survey methods by post or telephone.[236] HRQoL was assessed using the European Quality of Life–5 Dimensions (EQ-5D-3L) instrument,[194] which has been validated for stroke.[375] For each of the 5 dimensions of the EQ-5D including mobility, self-care, usual activities, depression/anxiety, and pain), there are three response categories: no problem, some/moderate, and extreme problem.

The EQ5D information was collected from patients or proxy respondents when patients were unable to respond to the interviewers. Unassessed survivors included

those who were lost to follow-up only after multiple contact attempts (non-responders) and the time from discharge was more than 180 days or the patient/proxy refused (non-consenters).

10.4.3 Statistical analyses

All these analyses were performed by Stata 12.1 (StataCorp Texas, 2011).[269] P values ≥ 0.05 were considered as statistically significant.

Utility scores were calculated by summing the component scores of each of the five EQ5D domains and adding value sets from relevant general populations to create an overall score using Australian population-based methods based on the discrete choice experiment (DCE).[376] The DCE approach was used instead of Time-Trade-Off technique as it was developed with a greater proportion of older people so it was more aligned with our stroke cohort. The utility score is a scale on which full health has a value of 1, while 0 indicates death and negative values indicate health states worse than death. The EQ5D score ranges from a negative score (worse than death) to 1 (perfect health). Those who died during the follow-up, assigned a score of 0 as per the instrument validation, and unassessed patients were excluded in our analyses.

Among stroke survivors, random-effects quantile regression accounting for individual hospital correlations was used to generate median differences in EQ5D utility score for women compared to men. Median regression was used as the EQ5D has a bimodal distribution or is highly skewed. Multivariable modelling was performed to examine the covariates (sociodemographics, stroke-related factors and in-hospital processes of care) that would potentially contribute to sex differences in EQ5D at 3-6 months after

stroke. Our model-building procedure was based on the purposeful selection of covariates.[207] The following criteria for being a confounding factor were applied to determine the covariates in the multivariable models: (1) the covariate was associated with sex; (2) the covariate was associated with outcome (EQ5D scores); and (3) the inclusion of the covariate in the model with only sex if it changed the magnitude of the sex coefficient by ≥10%.[207] Statistical interaction was assessed by a test of statistical significance of a sex x covariate product term. In further analyses of sub-domain scores of EQ5D, female:male relative risk (RR) of having any problem for each dimension was performed using log-binomial regression. Factors potentially associated with the sex differences in each sub-domain were also examined in multivariable models.

Sensitivity analyses were used to assess the effect of the multiple imputation by chained equations (m=50 imputations) and inverse probability weighting[377] to account for missing data with missing at random assumption on HRQoL and covariates on the results. The individual domain scores of EQ5D of missing data were initially imputed and subsequently converted into overall utility scores. This approach was justified as being more reliable in a large dataset (>500 cases) than directly imputing the overall utility score.[378]

In analyses comparing the AuSCR with population-level EQ5D, mean utility scores for stroke survivors were calculated within sexes and age groups (<55, 55-64, 65-74 and ≥75 years old). The corresponding utility EQ5D scores of the general population were obtained from the data of the South Australian population-based Health Omnibus Survey.[374] The survey provided mean EQ5D utility scores of the Australian

general population that are current and available by age and sex strata. We then calculated the weighted mean difference scores between AuSCR stroke registrants and the general population within each age group, separately for men and women.

A minimal clinically important difference represents the minimum benefits in the practice (from the treatment or other acute therapies).[78] The minimally important difference for EQ5D utility scores ranging from 0.08 to 0.12 units are reported in the stroke population.[277] In this study, therefore, any difference in utility between men and women greater than or equal to 0.08 was defined as clinically meaningful.

10.5 Results

Over a median follow-up of 139 days (IQR 123-161), there were 2700 deaths out of 14118 registered cases of stroke. About 60% (6852/11418) of survivors completed follow-up surveys with EQ5D assessment; 44% being female (**Table 10-1**). Among those with EQ5D assessment at 3-6 months after stroke (n=6852), compared to men, women registrants were 6 years older (median age: 77 years vs men 71; p<0.001), and less able to walk independently on admission (37.9% vs men 46.1%, p<0.001; **Table 10-1**). Women were more often discharged to aged care (5.1% vs 1.3%; p<0.001), and less often discharged directly home from acute care (44.1% vs 51.0%; p<0.001, **Table 10-2**). At median 139 days after stroke, women were more likely to live alone (25.8% vs 16.7%, p<0.001) and less likely to stay at home (87.5% vs 77.9%) than men. Proxy results for the EQ5D were obtained among 44% of available patients with a greater proportion for women than for men (46.3% vs 41.7%, p<0.019; **Table 10-2**).

The proportions of women were the same between those with and without assessment (44%). However, compared to those unassessed with EQ5D, assessed patients were older, had less severe strokes (indicated by the ability to walk independently on admission), and fewer intracerebral haemorrhages (**Appendix G**: **Supplemental Table G-1**). In the entire cohort (n=6,852; 39 hospitals), the assessed patients more often received processes of care including being treated in a stroke unit, aspirin administered ≤48 hours, and prescription of antihypertensive medication at discharge. In a subset of patients from Queensland (n=2,492; 21 hospitals), those with EQ5D assessment were more often mobilised and also had more dysphagia screening ≤24 hours than those without assessment (**Supplemental Table G-2**).

Sex difference in EQ5D domain scores among survivors

Women reported at least one problem in four EQ5D domains including self-care, usual activity, pain/discomfort and anxiety/depression more often than men (**Supplemental Table G-3a**). Further examination of the female:male relative risks showed that the sex differences were slightly attenuated by stroke severity but modified by age group. In all four domains, the effect estimates for sex were statistically significant among people aged 75 years and older. Anxiety/depression problems were also more prevalent among middle-aged women (65-74 years) than their men counterparts (**Supplemental Table G-3b**).

Sex difference in overall utility scores among survivors

Based on AuSCR data, the DCE utility scores ranged from -0.516 (worse than death) to 1 (perfect health). The median overall utility scores among survivors were 0.775 (IQR 0.576-0.887) and 0.693 (95% CI 0.482-0.887) for men and women, respectively. Women had poorer HRQoL compared to men at 3-6 months after stroke in unadjusted analysis (median difference; MD -0.082, 95% CI -0.099, -0.066) which bordered on the clinically meaningful threshold. Age and stroke severity accounted for about 50% of the sex differences and the adjusted MD (-0.039, 95% CI -0.056, -0.021) was below the clinically significant threshold. Further adjustment for 3-month place of residence further attenuated the sex differences (MD -0.029, 95% CI -0.052, -0.006). Neither clinical care nor the other factors including length of stay, discharge information, living alone status at 3 months, and proxy assessment confounded the sex difference in EQ5D utility in the multivariable models.

Sex difference in EQ5D utility scores between women and men survivors differed by age group ($p_{interaction}<0.001$) and severity of stroke ($p_{interaction}<0.001$). In the younger age group (<65 years old), there was no statistically significant difference in utility score between sex regardless of stroke severity although women survivors appeared to have slightly better scores (**Table 10-3**). By contrast, the direction of the association between sex and HRQoL was reversed in the older age groups. Elderly women aged 75^{+} with a severe stroke had lower utility scores after stroke than elderly men and the difference was clinically significant (MD -0.103, 95% CI -0.160, -0.047). Among survivors after a less severe stroke, older women also experienced poorer HRQoL than their men counterparts and the magnitude of the difference was about two times greater in the 65-74 age group than the oldest group (75^{+} years; **Table 10-**

3). Sensitivity analyses to account for missing data on EQ5D using multiple imputation with inverse probability weighting technique produced similar results when compared with complete-case analysis (**Supplemental Table G-4**).

Sex difference in HRQoL between people with and without stroke

Stroke caused clinically meaningful differences (CMD) in HRQoL across all age group but generally increasing with age. The magnitude of the loss was similar for men and women. Mean EQ-5D utility scores were significantly lower for people with stroke compared to the population norms across all age groups (mean difference ranged: 0.25 – 0.51), well above the clinically meaningful threshold (**Figure 10-1**). The magnitude of the sex difference was greatest among those aged 75^{+} years (utility mean difference: 0.44 for men vs 0.51 for women) but generally less than the CMD (<0.08). The analysis of the sex difference in utility scores compared between those with and without stroke showed that age modified the sex difference. Younger males were more like to have greater health loss due to stroke than their female counterparts (mean difference, aged <55: 0.31 vs 0.25; aged 55-65: 0.31 vs 0.30; **Figure 10-1**). On the other hand, older men often had lesser health loss caused by stroke than older women (mean difference, aged 65-74: 0.40 vs 0.35; aged 75^{+}: 0.44 vs 0.51).

10.6 Discussion

The differences between men and women in HRQoL at 3-6 months after stroke were explained by age, severity of stroke and 3-month place of residence. Young men and older women, particularly those with more severe strokes, had a poorer outcome. No

other factors including discharge destination, stroke care, and living alone status at 3-6 months contributed to the sex differences. Although stroke caused a significant health loss for both men and women, generally increasing with age, the magnitude of the sex differences in HRQoL between those with and without stroke was small across age groups.

Younger women with stroke had a slightly better self-reported HRQoL score than younger men although the difference was not statistically significant. Younger men had worse HRQoL compared to younger women which could be because they face a greater risk of cardiovascular diseases (e.g. higher prevalence of smoking) that were unavailable in our study and develop these diseases at younger ages than women. Rather than biological and genetic factors, which have been considered the traditional determinants for the sex difference, other covariates based on social context may also contribute to the poorer HRQoL among young men after stroke. Previous research showed that men who did not return to work at 6 months after stroke had substantially worse HRQoL than those men who returned to work while there were no detectable differences between women that did and did not return to work.[379] This could be related to the differences between men and men in self-perceptions of role (i.e. being a provider), and ability to work that are associated with HRQoL after stroke.[380]

By contrast, elderly women appeared to have poorer HRQoL after stroke than elderly men. This difference was statistically and clinically significant, particularly among those women with severe strokes. This can be due to the fact that women tend to be older, frailer and have more health problems when they develop stroke.[236] This means

that more women in the older age group experienced severe strokes and poorer functional outcome and participation restriction than their male counterparts that are associated with reduced HRQoL.[60] In our HRQoL sub-domain analyses using the AuSCR data, the elderly women generally had more pain/discomfort, anxiety/depression, as well as problems with self-care and usual activity after stroke than elderly men, consistent with previous research.[287,381] Thus, better identification and management of anxiety and depression after stroke, particular for women and the elderly in general may reduce these sex differences. There are some differences between men and women in coping strategies,[382] and imperative to life satisfaction,[383] that may differently affect their self-reported HRQoL following stroke. The level of self-efficacy that survivors have in their ability to function in daily life has been proven to influence well-being after stroke, particularly HRQoL.[384]

Walking ability at admission as a proxy for stroke severity was an effect modifier of the sex difference in HRQoL after stroke. The finding is somewhat consistent with our previous research whereby stroke severity (e.g. indicated by the National Institute Health Stroke Scale − NIHSS) contributed to the poor outcomes in women after stroke including HRQoL.[385] This suggests that although it might not be as sensitive as other severity scales (e.g. NIHSS), walking ability is reliably collected and serves as a good marker of stroke severity in predicting outcome.[236,329]

Our further comparison between stroke with stroke and normal norms revealed consistent results whereby stroke caused a greater HRQoL loss for younger men than younger women, but the direction of the association with sex was reversed for older

people. However, the net differences in utility scores between those elderly women and men with and without stroke were below the clinically meaningful threshold. This suggests that sex differences in HRQoL after stroke were not only caused by stroke but also due to other existing sex differences. Future studies should consider the existing differences in HRQoL between men and women when reporting results of sex differences in HRQoL after stroke and associated factors. Factors contributing to sex differences in the level of HRQoL in people without stroke could include the presence of chronic health conditions or depressive symptoms which have a stronger negative impact on HRQOL in female patients than male patients in the same age group.[386] Although we were unable to examine these due to the lack of data on comorbidities and mood disorder, our analyses on the EQ5D subcategory of depression/anxiety data suggest that women face more problems on mental health compared to men.

These findings have several implications for practice and research in stroke to improve HRQoL for both men and women. The large impact of age on the association between sex and HRQoL after stroke highlights an imperative of improving health for the elderly, who are mostly women. Given the important role of stroke severity in the association between sex and HRQoL, better management of the modifiable factors of stroke severity should reduce the sex difference. Promotion of active healthy aging to increase years lived in healthy life is of utmost importance.[281] Strategies to reduce risk factors for cardiovascular diseases (CVD), which are more prevalent in men, such as smoking need to be addressed to narrow the gender gap in the younger age group. Other non-traditional predictors of CVD in young males (e.g. pattern baldness and

premature greying)[387] are possibly helpful to detect diseases at an early stage but further research is required. Developing more effective primary prevention strategies to reduce health differences according to age and sex should also be a priority.[280] These programs need to better target people with different levels of CVD and stroke risk, particularly providing more supports for those who are more vulnerable to stroke including young men and old women.

When prevention fails and stroke happens, all efforts to reduce the impact of stroke should be taken. We found that a number of men and women with strokes were not treated with evidence-based therapies such as stroke unit care (>10%) and intravenous thrombolysis for ischaemic stroke (88%). It is important to ensure greater access to evidence-based processes of care (i.e. stroke unit care, thrombolytic therapy, antihypertensive agents, and care plan at discharge) for those with stroke, regardless of sex, that are associated with better HRQoL.[236] It is also necessary to prevent the development of anxiety and depression which can significantly influence the recovery after stroke, particular for the elderly. Other individual or social factors (e.g. race, ethnicity, and culture), clinical indicators and post-stroke conditions (e.g. living alone) that are associated with poorer HRQoL should be taken into account when setting up rehabilitation and intervention programs.[280]

The magnitude of the sex difference in EQ5D utility overall scores at 3-6 months after stroke was small and consistent with previous research with the EQ5D instrument.[110] Although EQ5D has been well-validated for use in stroke, the generic instrument of HRQoL may exclude some domains that differ by sex (e.g. family role, social

interactions, relationships, self-perception, memory),[287,388,389] or are specific to stroke (e.g. communication, sexual function). Therefore, the sex difference in HRQoL might be underestimated when using EQ5D when compared to other generic instruments (e.g. Short-Form 36 questions; SF36) or stroke-specific instruments (e.g. Stroke-Specific Quality of life; SSQoL). For example, according to the Paul Coverdell National Acute Stroke Registry (US), women had significantly lower SSQoL overall scores and on various sub-domains, including physical function, thinking, language, energy, mood and role function, even after accounting for covariates.[104] Further comparison of the sensitivity of HRQoL instruments and qualitative studies that focus on the sex difference will provide better targets for intervention (e.g. social support) to mitigate the sex difference in HRQoL after stroke, particularly for vulnerable groups.[388]

A number of the study's strengths need to be acknowledged. The study was based on a large dataset obtained from 39 hospitals across five states of Australia with a standardised data collection to ensure data quality and adequate power to test our hypotheses. Another strength of the AuSCR is the follow up on over 6,500 cases. By using a national registry with stroke performance indicators aligned with current recommendations (i.e. level-1 evidence of impacting outcome), this study provides a value-added contribution to the clinical practice and current literature of whether there are sex differences in stroke care in Australia and its association with HRQoL. Our results of the sex difference in HRQoL between people with stroke and without stroke help fill the gap left because very few studies attempted to examine the loss of HRQoL by stroke[21,123] and, to our knowledge, none of these specifically aimed to

focus on the sex difference. By determining factors that explain sex differences in HRQoL, this study provides the evidence basis for future research and intervention development to improve outcomes after stroke for both men and women and, in turn, reduce the burden of stroke on health systems and communities.

Several limitations should be acknowledged in this study. The generalisability of the study results may be restricted by the fact that patients from the AuSCR hospitals appeared to have better care for stroke compared to the current experience of the general stroke population according to the national data.[345] However, this is less likely to substantially affect our conclusion since sex differences in access to care did not account for the difference in HRQoL after stroke. The mean score of EQ5D (0.64, SD 0.33) in the AuSCR dataset was closely similar to those from other developed countries (e.g. the United Kingdom, the United States), falling on the lower end of the global range (**Supplemental Table G-6**), suggesting that our results may reflect the experience of stroke patients in different settings. The minimal clinically important difference (MCID)[78] has been performed to determine the benefits of an intervention or changes over time rather than designed to assess sex differences. Although the sex differences in this study were small, our findings may be biased because the MCID in EQ5D utility score for stroke population (0.08-0.12)[277] was used to define the clinically meaningful difference between sexes. Our findings suggest that poorer quality of life in elderly women compared to men was due to stroke and other sex differences in the population, but the lack of detailed data (i.e. comorbid diseases, pre-stroke function) prevented us from more in-depth analyses of the potential sex difference effects of these factors on the HRQoL. Other post-stroke factors such as

rehabilitation outcomes and pain, depression and its treatment were not assessed in this registry. Gathering the data from multiple sources and linking the data across sources (e.g. AuSCR, medical records, and rehabilitation services) would provide insight for future work to examine the role of these factors in the sex difference in HRQoL. Compared with those unassessed, assessed patients were older, had fewer haemorrhages, less severe strokes, and more often received acute stroke therapies. However, this was less likely to substantially affect our conclusion since people with and without assessment were similar in their gender distribution (44% being female) and the other factors (stroke type and evidence-based therapies) did not account for the sex difference in HRQoL. Although the results of sensitivity analyses accounting for missing data using imputation combined with inverse probability weighting technique showed almost no change, we cannot fully preclude the selection bias particularly the age difference between those assessed and unassessed.

Conclusion

Women generally had worse HRQoL after stroke than men in unadjusted analyses. Young men with stroke appeared to have slightly lower HRQoL utility scores at 3-6 months than their female counterparts. By contrast, elderly women with stroke had significantly poorer HRQoL after stroke compared to elderly men but the difference was modified by stroke severity. The worse HRQoL after stroke among younger men and older women was largely due to stroke, but was also associated with other sex-related health differences existing in the population. These findings highlight the importance of more effective prevention strategies to improve the general health for

people across different levels of stroke and CVD risk factors as well as ensuring evidence-based acute care and post-stroke management, particularly for women and the elderly with more severe strokes more generally.

Table 10-1. Characteristic of AuSCR registrants for first−ever stroke during 2010−2014 having EQ5D assessment at 3-6 months after stroke (n=39 hospitals)

	Survivors with EQ5D assessment (n=6,852)		
	Men	Women	p−value
	N (%)	N (%)	
Number of cases	3821 (55.8%)	3031 (44.2%)	**<0.001**
Sociodemographics			
Age, median (IQR)	71.2 (62.0−79.5)	77.1 (65.7−84.4)	**<0.001**
State			
New South Wales	618 (16.2%)	436 (14.4%)	0.529
Queensland	1388 (36.3%)	1104 (36.4%)	
Tasmania	235 (6.2%)	189 (6.2%)	
Victoria	1375 (36.0%)	1150 (37.9%)	
Western Australia	205 (5.4%)	152 (5.0%)	
Socioeconomic position			
IRSAD1	618 (16.2%)	482 (15.9%)	0.529
IRSAD2	822 (21.5%)	651 (21.4%)	
IRSAD3	522 (13.7%)	393 (13.0%)	
IRSAD4	819 (21.4%)	645 (21.3%)	
IRSAD5	1040 (27.2%)	860 (28.4%)	
Born in Australia	2562 (67.1%)	2153 (71.0%)	0.070
Aboriginal or Torres Strait Islander	46 (1.2%)	31 (1.0%)	0.594
Stroke−related factors			
Transfer from other hospital	561 (14.7%)	399 (13.2%)	0.174
Stroke while in hospital	165 (4.3%)	150 (5.0%)	0.236
Time (minutes) from onset to arrival, median (IQR)	192 (83−701)	207 (83−742)	0.273
Walking independently at admission (proxy for stroke severity)*	1653 (46.1%)	1077 (37.9%)	**<0.001**
Cause of stroke known	1901 (50.5%)	1419 (47.4%)	**<0.001**
Type of stroke			
Intracerebral haemorrhage	414 (10.8%)	355 (11.7%)	0.505
Ischaemic stroke	3309 (86.6%)	2587 (85.3%)	
Undetermined	97 (2.5%)	89 (2.9%)	

IRSAD = the Index of Relative Socio-Economic Advantage and Disadvantage
*stroke severity was defined as unable to walk independently on admission

Table 10-2. Processes of care, discharge information and longer term outcomes for first−ever stroke in the AuSCR during 2010-2014

	EQ5D assessed (n=6852)		
	Men	Women	P−value
	N (%)	N (%)	
Discharged information			
Length of stay if discharged, median (IQR) days	5 (3−8)	5 (3−9)	1.000
Discharge destination			
Died in hospital	–	–	
Aged care	61 (1.3%)	155 (5.1%)	**<0.001**
Home	1950 (51.0%)	1337 (44.1%)	
Rehabilitation	1324 (34.7%)	1142 (37.7%)	
Hospitals/other	486 (12.7%)	397 (13.1%)	
Evidence−based therapies			
Treated in stroke unit	3358 (87.9%)	2647 (87.3%)	0.835
Intravenous thrombolysis*	436 (13.3%)	315 (12.3%)	0.298
	436 (33.0%)†	315 (35.6%)	0.175
Care plan on discharge to community	1100 (54.7%)	782 (52.4%)	0.280
Discharged on antihypertensives	2834 (74.9%)	2254 (75.1%)	0.986
Data between 3-6 months (self-reported)			
Current residence			
Aged care	255 (6.7%)	479 (16.0%)	**<0.001**
Home	3307 (87.4)	2338 (77.9%)	
Rehabilitation	65 (1.7%)	29 (1.0%)	
Hospitals/other	158 (4.2%)	157 (5.2%)	
Living alone‡	628 (16.4%)	768 (25.3%)	**<0.001**
Having recurrent stroke‡	155 (4.1%)	138 (4.6%)	0.314
Proxy EQ5D assessment§	1109 (41.7%)	968 (46.3%)	**0.019**
Readmission	730 (19.1%)	569 (18.8)	**0.727**
Additional process of acute care indicators (Queensland patients only)	n = 1388	n = 1104	
Mobilisation ≤48 hours if unable to walk on admission	463 (66.2%)	404 (63.1%)	0.765
Received swallow assessment ≤24 hours	819 (59.0%)	602 (54.5%)	0.094
Aspirin administration ≤48 hours*	894 (73.1%)	643 (66.3%)	0.245
Discharged on antiplatelets or antithrombotic*	960 (82.3%)	715 (77.4%)	0.556

* among ischaemic stroke
† among those with admission time ≤3.5 hours
‡ missing data <10%
§ missing data: 31%

Table 10-3. Difference in EQ5D scores between women and men survivors at 3-6 months after stroke according to age group and stroke severity*

Age group	Unable to walk					Able to walk				
	Men		Women		Women vs men	Men		Women		Women vs men
	n	Median (IQR)	n	Median (IQR)	MD (95% CI)	n	Median (IQR)	n	Median (IQR)	MD (95% CI)
<65	555	0.697 (0.490, 0.887)	334	0.697 (0.572, 0.887)	0 (-0.035, 0.035)	595	0.800 (0.663, 0.887)	338	0.810 (0.683, 0.887)	0.010 (-0.024, 0.043)
65-74	530	0.706 (0.482, 0.887)	326	0.689 (0.482, 0.879)	-0.018 (-0.053, 0.017)	497	0.887 (0.693, 0.887)	246	0.800 (0.689, 0.887)	**-0.087 (-0.131, -0.043)**
>75	847	0.679 (0.459, 0.887)	1104	0.586 (0.198, 0.784)	**-0.103 (-0.160, -0.047)**	561	0.800 (0.663, 0.887)	493	0.766 (0.572, 0.887)	-0.034 (-0.072, 0.003)

CI = confidence interval; IQR = interquartile range; MD = median difference

*more severe stroke = unable to walk without assistance on admission; less severe stroke = able to walk without assistance on admission

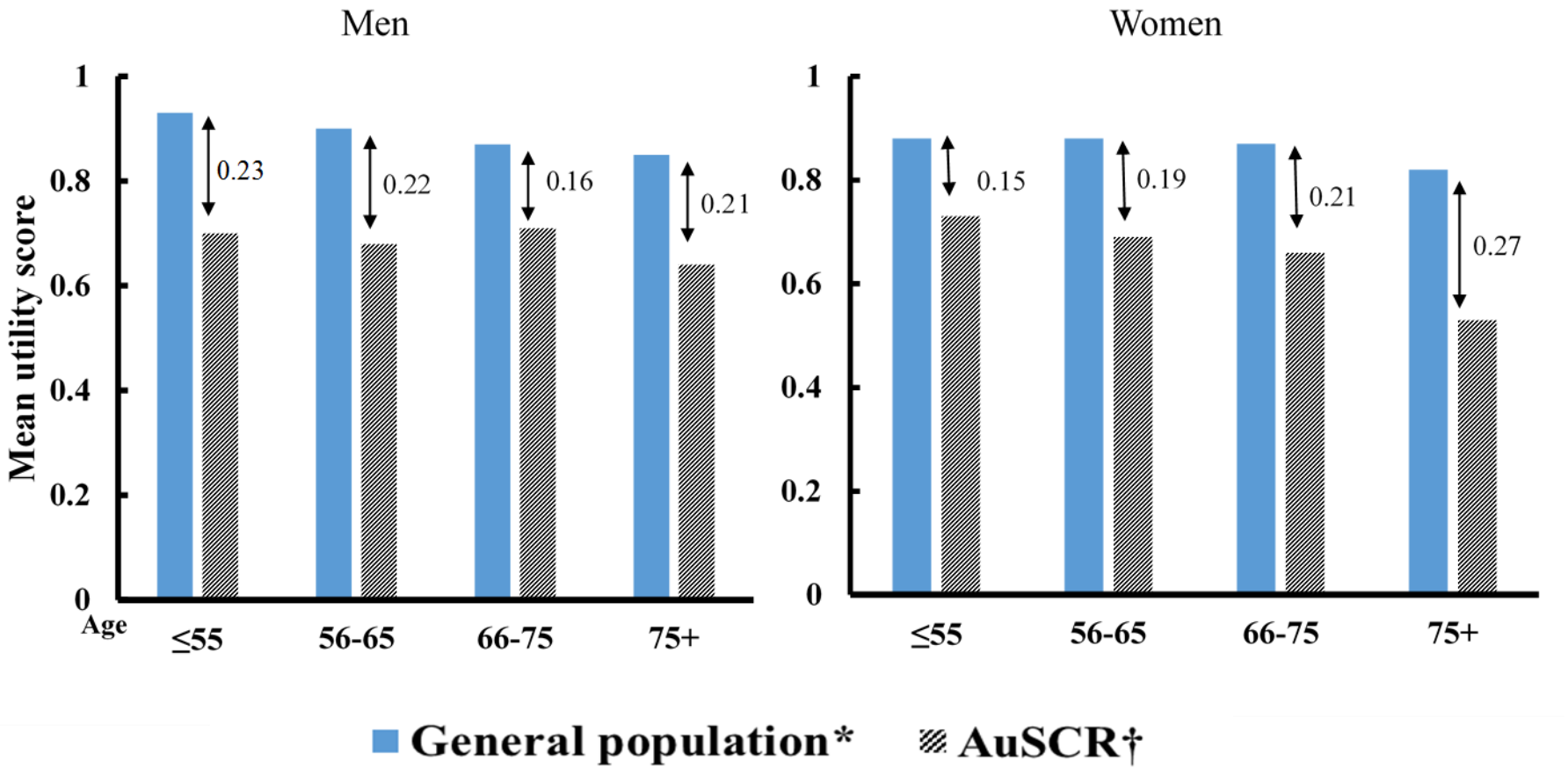


Figure 10-1. Mean difference in EQ5D utility scores between AuSCR survivors and the general population
*** from McCaffrey et al (2016); the score for group <55 was used by weighted estimates from age 15−54**
† AuSCR registrants who survived to 3-6 months after stroke

Chapter 11: Summary, implications, and future directions

My thesis examined a series of research questions to comprehensively investigate the causes of sex differences in stroke management and outcomes after stroke. This work provides an original and significant contribution to the current literature on potential targets to mitigate the differences. In the papers produced as a consequence of completing this body of work, I substantially contributed to the study concept and design; the acquisition, analysis, and interpretation of data; and the preparation of the manuscripts for publication in peer-review journals.

The results are likely to be relevant to people with stroke in many different settings given the use of individual participant data (IPD) that I compiled and analysed on first-ever strokes from 13 high-quality population-based studies (INSTRUCT; n >16,900 cases) conducted in many regions of the world, as well as data from a national stroke registry (AuSCR; n >14,000 cases). The two datasets complemented each other in addressing potential strengths and weaknesses of their designs (**Table 11-1**) while also addressing several limitations of the existing literature.

There were several novel aspects to the study designs that add to the overall quality of my research. The use of the two-stage method for IPD meta-analyses overcame inconsistent definitions and measurements of outcomes and covariates between different studies in the INSTRUCT. The data came from high-quality and generalisable studies with a very large number of participants, making this study adequately powered to test our hypotheses. Many investigators did not report sex-

specific outcomes (section 1.3),[170,173,369-373] my study approach could have helped address the issue that many investigators did not report sex-specific outcomes[173] which may be due to limited sample size or lack of awareness of the need of reporting results stratified by sex.[390] I examined the sex differences in a wide range of long-term outcomes after stroke available in the INSTRUCT including all-cause mortality, functional outcome, participation restriction, and HRQoL. The AuSCR analyses added substantially to the research through contributions on mortality, including COD, and HRQoL outcomes. Further, the data on stroke management in the AuSCR were up to date, so that the results are highly relevant to current clinical practice. In both datasets, the factors contributing to the poorer outcomes in women after stroke were investigated using purposeful model building, rather than traditional step-wise methods, providing a more comprehensive understanding of these factors than available from most of the previous studies.

The findings fill important gaps in our understanding of why women have worse outcomes after stroke. They are likely to inform clinical practice, the development of new interventions and future research. A summary of the major findings is provided here, along with the potential implications and future directions for research.

Table 11-1. Strengths and limitations of the two datasets: the INternatinal STRoke oUtCome sTudy (INSTRUCT) and Australian Stroke Clinical Registry (AuSCR)

	INSTRUCT	AuSCR
	Strengths	
Study design	Population-based	National registry with standardised data collection
Analytic method	Individual meta-analysis of large dataset (two-stage approach) with modelling that specifically focused on sex differences	Multilevel modelling, accounting for hospital clusters, that specifically focused on sex differences
Measures of outcomes	A wide range of patient-reported outcomes were assessed.	Survival status was accurate as linked to national death registrations data.
Measures of covariates	A wide range of covariates were assessed.	The data on stroke management were up to date, so that the results are highly relevant to current clinical practice.
	Limitations	
Study design	Many studies were conducted in high-income countries.	The research was based in the acute hospital setting and did not include all eligible hospitals across Australia and the number of clinical process indicators was minimal (4-8 max) whereby we

		may over-/under-estimate the sex difference clinical care associated with longer term patient outcomes.
Measures of outcomes	There were fewer eligible studies with data on long-term functional outcome and HRQoL with various outcome measures.	There were no data on functional outcome.
Measures of covariates	Data on stroke management stroke were limited and outdated.	There were no data on history of cardiovascular diseases.

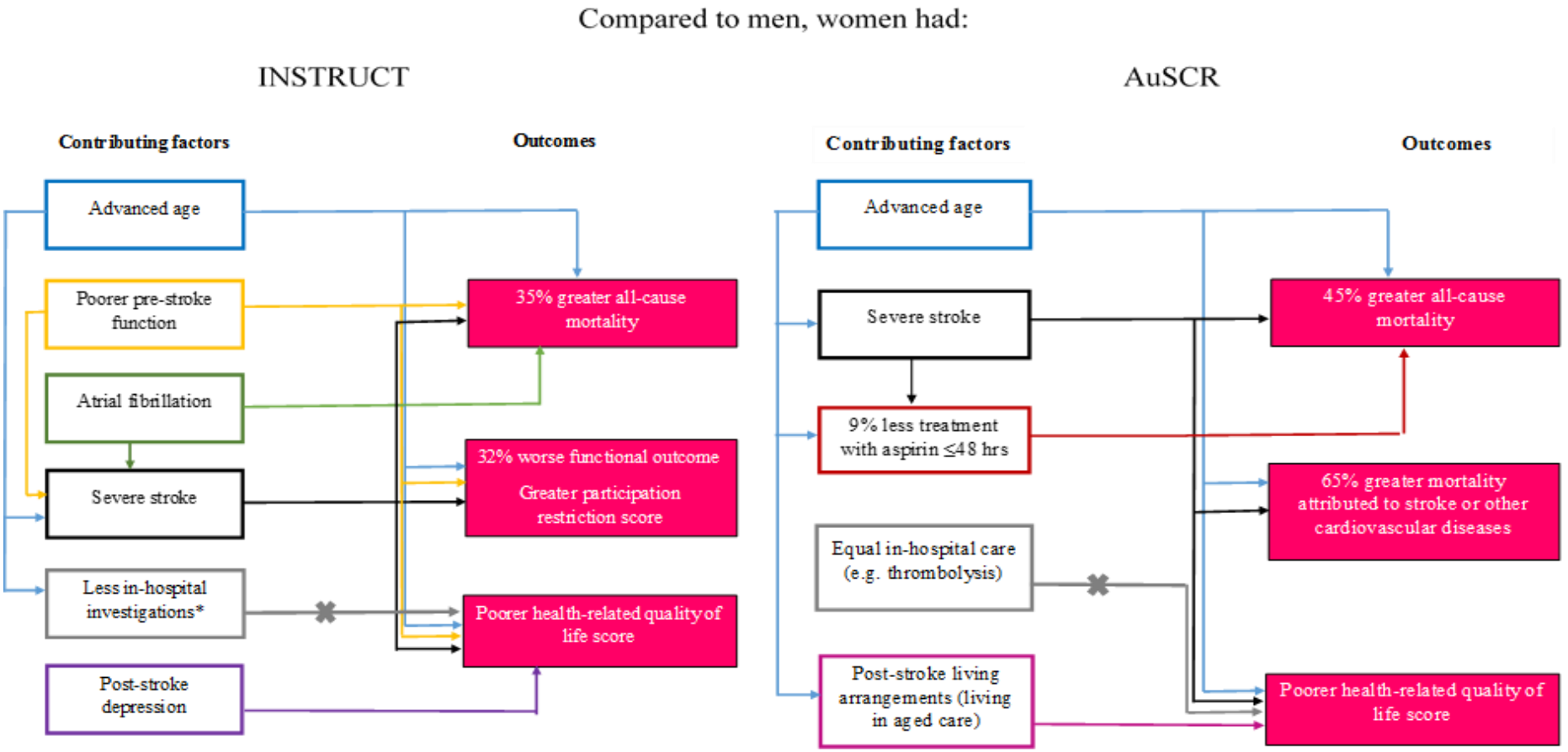


Figure 11-1. Summary of contributing factors to the sex differences in outcomes up to 5 years after stroke using the data from 13 population-based studies (INSTRUCT) and the Australia Stroke Clinical Registry (AUSCR). *denotes carotid investigation or echocardiography

11.1 **Summary of major findings**

In **Chapter 3,** I presented that women were 35% more like to be deceased by 1 year and 24% by 5 years after stroke compared to men. The poorer survival after stroke in women was fully explained by their advanced age, worse pre-stroke function, more severe stroke and, to a lesser extent, the presence of atrial fibrillation.

In **Chapter 4**, I showed that up to 5 years after stroke, women were 31-32% more likely to have poorer functional outcomes and greater participation restriction than men. These worse outcomes after stroke among women were mostly explained by age, stroke severity, and poorer pre-stroke function.

In Chapter 5, women, compared to men, were found to have 0.09-0.15 point lower mean utility scores up to 5 years after stroke, regardless of the HRQOL instrument (i.e. EQ5D, SF6D or AQoL). The poorer HRQoL after stroke in women was mostly explained by advanced age, pre-stroke functional limitations, stroke severity, and to a lesser extent, the presence of post-stroke depression. The innate differences between men and women in the general population were also explored providing potentially important context to the sex difference in HRQoL after stroke.

In findings detailed in **Chapters 3-5** (using the INSTRUCT data), women less often received in-hospital investigations including echocardiography and carotid investigation than men. However, these differences in care did not contribute to the sex differences in long-term outcomes after stroke.

Stroke severity was presented as a key factor contributing to the sex differences in survival, functional outcome, and HRQoL (Chapters 3-5). As such, severity was considered as a separate endpoint in **Chapter 6.** There was a 35% increased risk of having severe ischaemic strokes (NIHSS>7) in women than men. The sex differences in stroke severity were mostly explained by age, pre-stroke dependency, and atrial fibrillation. There was no sex difference in severity for intracerebral haemorrhage, even after adjustment for covariates.

In **Chapter 8**, using data from the AuSCR, I demonstrated that there were only minor differences between men and women in the care received in the hospital. This was across several important evidence-based aspects of care including stroke unit access, intravenous thrombolysis, care plan provided at discharge, and being discharged on antihypertensive agent(s). Results for sex differences in outcomes were very similar to those using the INSTRUCT dataset. Women were 45% more like die by 1 year after stroke compared to men. The greater mortality in women was fully explained by age and stroke severity (indicated by the ability to walk independently on admission) but not due to the differences in processes of care

Additional data from a subset of hospitals in Queensland, did indicate that women were 9% less likely to be administered aspirin ≤48 hours than men. In this subset, older age, severity, and under-treatment with aspirin, contributed to the sex differences in 1-year mortality.

In **Chapter 9**, I reported that mortality up to 1 year after stroke was mainly driven by stroke and other cardiovascular diseases using the data from the AuSCR. Among those with stroke, causes of death (COD) up to 1 year following stroke differed by

sex. Women had 65% greater risk of death due to stroke or other cardiovascular disease (CVD; not including IHD) than men. These sex differences were mostly explained by age and stroke severity, indicated by the ability to walk on admission. In contrast, men with stroke were more likely to die by 1 year after their stroke from cancer or IHD than women. Both men and women across age groups had excess mortality due to stroke (>8 times higher than expected), IHD and other CVD (~3 times higher) and cancer (2.6 times higher) compared with the general population.

In **Chapter 10**, I found that women with stroke had, on average, 0.08 point lower HRQOL mean utility EQ5D scores at 3-6 months after stroke than men. Age, stroke severity, and living in aged care at 3 months post-stroke explained part of the sex differences but the younger men and elderly women still had poorer HRQoL after accounting for these factors. None of the differences in processes of care contribute to the sex differences in HRQoL. As was found in the comparison with the general population in the INSTRUCT data, the innate differences between men and women in HRQoL also accounted for some of the sex difference in HRQoL.

A summary of the main results are illustrated in **Figure 11-1**.

11.2 Implications and future directions

In the thesis, I have provided a comprehensive examination of the causes of differences between men and women in outcomes after stroke. Although most of the differences were explained by covariates, this does not mean that there is no sex difference. We cannot deny that women present at older ages with more severe strokes, and then have poorer outcomes that persist into the long term following stroke compared to men. Our research findings show that several factors including age, pre-stroke function, atrial fibrillation, stroke severity, and mood come together to contribute to a worse outcome for women (Figure 11-1). There were only minor variations in stroke care between men and women which reflects the overall advances in stroke care in recent times. Indeed the lack of differences across nearly all aspects of stroke care are indicative of the success of efforts to systematically monitor and improve the quality of stroke care. The findings of this thesis have a number of important implications for public health and clinical practice to minimise the gender gap in stroke outcomes.

11.2.1 Factors contributing to sex differences in outcomes after stroke

11.2.1.1 Age

The majority of poorer outcomes among women with stroke were explained by their advanced age compared to men. In the INSTRUCT data, women with stroke were older (mean age of 75.4 years (SD 13.9) compared with men 70.9 years; SD 13.3). Over 69% of all participants aged 85 years or older in the dataset were women. These figures suggest that reducing the burden of stroke in the elderly will attenuate the sex

differences. Older age may reflect the reduced functional capacity of brain cells to recover after neurological insults,[212] and other age-related factors including frailty, comorbidities (e.g. atrial fibrillation, hypertension and diabetes), functional limitations, and social isolation,[213] which then lead to worse outcomes after stroke.

Better stroke prevention by targeting modifiable CVD risk factors, prevention of frailty,[220] and clinical management in the elderly, who are mostly women, are needed to improve cardiovascular and general health. This type of prevention will promote healthy active ageing and increase the years lived in healthy life.[281] In Australia, annual health assessments for all people aged ≥75 years and older have been included in Medicare Benefits items since 1999.[391] However, the uptake of these health checks among older Australian (75^{+}) from 1999 until 2010 was general low (approximately 20%) and slightly higher for women than men.[392] In the Australian Longitudinal Study on Women's Health, although there was an increase in assessment uptake in older women but many women either did not receive an assessment or did not repeat it annually.[393,394] In addition, those older women in rural and remote areas were particularly disadvantaged.[393] This suggests a need for more programs in primary care settings for older people, particularly women in rural areas, to closely monitor health issues and respond early to their needs. For instance, preventive primary care outreach (PPCO) interventions among community-dwelling older people can reduce their mortality risk by 17%, according to a meta-analysis of 19 randomised controlled trials.[395] These outreach interventions are based on proactive, provider-initiated care in addition to usual care.[395] PPCO can be provided by physicians, nurses, other

professionals, or volunteers including home visits, office visits, telephone contacts, or a combination of these methods.[395]

On the other hand, men face a greater risk of having CVD including stroke at younger ages than women. There are therefore opportunities for more effective primary prevention aimed at preventing, or delaying, the onset of CVD and stroke in men, particularly younger men. This would also help narrow the gender gap in outcomes after stroke. Potential methods to achieve this would be better management of modifiable CVD risk factors including smoking cessation and promoting healthy lifestyle (i.e. healthy diets, physical activity and exercise), so that we can maximise stroke-free years of life.[396] In Australia, the Medicare 45 Year Old Health Check (MBS Item 717) has been available since 2006 for people aged 45-49 years who are at risk of developing chronic disease.[397] Middle-aged women, compared to their men counterparts, are at lower CVD risk and the health check program is less likely to be cost-effective.[398] However, the rate of services claimed by 2009 per 100 population aged 45–49 years did not greatly differ between men than women (6.8 vs 6.6).[397] Men have been reported to uptake health assessment less often than women, which are associated with such factors as the fear of getting the disease, avoidance of femininity, and lack of time.[399] Clinicians, researchers and policy-makers who are developing interventions and policies should be aware of these barriers to increase assessment uptake among men particularly those in middle age,[399] as well as engage them with healthy behaviours.[400]

There is evidence that older adults less often receive evidence-based stroke care than younger people.[214,401] This may contribute, among other factors, to their worse

outcomes after stroke compared to younger people.[401] Less receipt of some aspects of care in the elderly with stroke may be appropriate due to contraindications, side effects, or risk of complications of treatment.[216] Others have suggested that even older persons free of contraindications still receive less care than younger people.[402] A contributing factor may be that evidence regarding the best care is limited by the under-representation of elderly in clinical trials.[403] Also, costs of treatment might be an issue for the elderly because they may have less disposable income than younger people to pay for expensive prevention therapies. For instance, Australian consumers face high out-of-pocket costs which accounted for one-fifth of all health care spending.[404] According to an Australian Bureau of Statistics survey, about one in 20 people did not see a general practitioner due to cost, and the proportion was higher for women compared to men (5.2% vs 2.8%).[405] Some researchers have suggested that an 'age-bias' may exist,[406] whereby the patients' age (consciously or subconsciously) can influence clinicians' decision-making.[214] There has been an increasing interest in unravelling the age differences in management and outcome following stroke, but most studies have focused on rehabilitation settings[407,408] which may lead to some selection bias. More high-quality population-based studies specifically designed to examine the age differences in use or underuse of therapeutic interventions and long-term outcomes after stroke are needed to address these gaps. The data on age differences could be then incorporated into clinical guidelines including the safety and efficacy of interventions for older patients with stroke.[355] Further qualitative research to better understand how age-related complexities (e.g. multimorbidities, polypharmacy, or health costs) affect clinical decision-making may offer some solutions to minimise age and sex differences in care.[409]

When prevention fails and a stroke does happen, it is important to ensure access to evidence-based processes of care for all people with stroke, irrespective of their age or sex. There has been recent interest in 'care bundles', which assess combinations of in-hospital care, as they are associated with better survival and HRQoL.[60] A care bundle includes several evidence-based interventions for a defined patient population that is hypothesised to result in significantly better outcomes than when implemented individually.[410] For instance, receiving acute stroke unit care (ASU) combined with antihypertensive medication significantly improved 180-day survival more than ASU care alone.[60]

Poorer outcomes in elderly people may reflect a lack of intensive treatment due to the patient's and their family's preference as part of end-of-life care. However, the perspectives of end-of-life care are rarely recorded in current stroke studies and differences by sex have not been explored. Irrespective of age or sex, further investigations are needed to identify the needs of palliative and end-of-life care in order to provide adequate care and support for stroke patients and their families.[331,332] There has been recent discussion regarding the need to integrate palliative care within stroke services.[411] Quality improvement programs and patient outcomes in palliative care practices also warrant future stroke research. Increasing our understanding of effective treatments and ensuring access to them for the elderly, and indeed in people of all ages, should be aligned with patient and family preferences.

In summary, the overwhelming importance of age in explaining the sex difference suggests that better stroke prevention and access to evidence-based care for

cardiovascular and general health in the elderly is paramount to reducing the overall burden of stroke in men and women.

11.2.1.2 Functional limitations before stroke

Worse outcomes in women were also partly explained by their pre-stroke functional limitations, regardless of the measure used (i.e. self-reported mRS, Barthel Index and residing in a care facility before stroke). People with these type of functional limitations before stroke are more often women, older, and those having more cardiovascular comorbidities.[227,296] Having a functional limitation can impact referral to rehabilitation[246] and affect functional recovery after stroke.[247]

My analysis of the association between pre-stroke function and sex difference in outcome after stroke was limited by the use of crude measures of functional limitations (i.e. mRS). Future studies using more detailed frailty indices might advance our understanding of the impacts of pre-stroke health on outcome and management in men and women after stroke.[412] There are differences between men and women in the specific causes of healthy life lost. In men, they are mostly respiratory and cardiovascular conditions, whereas in women, they are most often musculoskeletal or related to mental disorders.[218] It is possible that better management of chronic disease targeting these conditions could improve function[219] and thereby to maximise recovery from stroke for both men and women, if it were to occur.

11.2.1.3 Stroke severity

Stroke severity was a prominent contributor to the sex differences in outcomes following stroke including mortality, functional outcome and participation restriction and HRQoL. Pre-stroke factors including age, pre-stroke functional limitation, and atrial fibrillation explained much (36%) of, but not all, the differences in stroke severity between men and women. The residual discrepancies may be due to unmeasured confounding factors but also underlying mechanisms of the more severe stroke in women, which requires further investigation. This should include both human and animal models to determine the potential biological reasons for the differences.

Stroke severity contributed to sex differences in outcomes after stroke including mortality, functional outcome and participation restriction and HRQoL. Acute interventions such as intravenous thrombolysis or endovascular clot retrieval are proven to lessen stroke severity, and improve outcomes following stroke.[355] Women with acute stroke appeared to receive thrombolysis[162] and endovascular treatment[330] less often than men although these therapies are equally safe and effective to obtain good outcome between the sexes.[413,414] Some of the sex differences are potentially explained by confounding factors (e.g. age and pre-stroke function), which requires further research to understand how these affect treatment and outcome after stroke. It is important to ensure equitable access to effective treatments of acute stroke for men and women to achieve more equal outcomes after stroke. An alternative way to reduce the severity of stroke, and therefore improve outcomes for women, might be to better manage the modifiable factors for stroke severity.[227] These are reported to

include hypertension, diabetes, and particularly atrial fibrillation that are more often prevalent in women with stroke than men.[236,415,416]

11.2.1.4 Atrial fibrillation

In my thesis, atrial fibrillation (AF) was found to contribute to the sex difference in more severe stroke and greater long-term mortality following stroke. Although women have a lower age-adjusted incidence of AF than men; their longer life expectancy results in the same lifetime risk of AF.[417] This results in a higher absolute number of women than men with AF.[418] Women with AF face a greater risk of stroke.[222] It is therefore surprising that they appear to have suboptimal management of AF compared to men.[419] This includes that women with AF are less often treated with anticoagulants[223] and receive less rhythm-control treatment (i.e. electrical cardioversion and catheter ablation) compared to men.[224] Importantly, these treatments are equally effective at reducing cardiovascular events including stroke among men and women with AF.[223,224]

It is important to ensure equitable identification of AF and access to effective therapies for men and women, with this likely reducing some of the sex difference in outcomes after stroke.[256,418] Some of the differences in treatments may be explained by women's greater age and co-morbidities that might lead to contraindications for some treatments.[420] Those aged ≥75 years with AF have an increased risk of haemorrhage than their younger counterparts but there is no clinically justifiable reason not to prescribe treatments based on older age alone. The issue of greater frailty, fragility, risk of falls, and polymedication in the elderly, many of whom are

women, may lead to their underuse of anticoagulant therapy.[421] Another possibility is the presence of cognitive impairment in elderly people, which is associated with their low adherence to AF treatment.[422] Identifying potential barriers to effective treatment of AF in women, and the elderly in general, and developing interventions to address this will help to reduce the burden of stroke.[419] For example, doctors might not prescribe warfarin in older women with AF if they are at risk of frequent falls but the effect of anticoagulation may not exceed the risk of intracranial haemorrhage.[419] Novel direct oral anticoagulants (NOAC) may, therefore, offer a solution given their risk of bleeding is much less compared to warfarin.[419] The NOACs are also reported to have fewer interaction with other drugs which can help increase medication adherence among the elderly.[419] Some of these new anticoagulants are more cost-effective than warfarin in preventing stroke and other cardiovascular events among those with AF (i.e. apixaban is optimal for those age ≥75 years).[423]

11.2.1.5 Processes of care

One of the greatest opportunities to improve outcome after stroke is to ensure access to evidence-based processes of care as recommended in clinical guidelines.[60] There is some evidence that if hospitals provided care in line with clinical guidelines, the health and economic benefits of reducing impacts of stroke would be substantial within the Australian context.[424] One way to increase the use of evidence-based care is through quality improvement programs that aim at changing clinical practice and increasing adherence to evidence-based clinical guidelines.[425-428] These have been shown to reduce variation in stroke care and therefore provide a way to reduce differences in outcome for many patient groups including women and the elderly.[429]

There were only minor variations in stroke care between men and women which could be interpreted as a success of efforts to systematically monitor and improve the quality of stroke care. Even though the differences are small and largely not statistically significant, the volume of patients with stroke might mean they may have a large impact on the total stroke burden. More importantly, a large number of both men and women with strokes were not treated with evidence-based therapies including stroke unit access, intravenous thrombolysis for ischaemic stroke, and secondary prevention medication. We should continuously strive to provide access to evidence-based care irrespective of a person's sex, age or where they live.[430]

11.2.1.6 Receipt of aspirin within 48 hours

The findings reported in this thesis highlight that early aspirin is important for women to access. Age and severity did not fully account for the under-treatment with aspirin among women. Further quantitative and qualitative research will be needed to explore the reasons for this difference. It is uncertain whether the sex difference in the use of this medication is due to unmeasured factors including comorbidities, medications, complications, or contraindications to the treatments (i.e. allergy, bleeding disorder, or uncontrolled hypertension).[336] The greater presence of comorbidities in women compared to men, particularly AF, may play a role whereby those women may receive anticoagulants instead of antiplatelet agents like aspirin.[333] However, in previous observational studies the underuse of both anticoagulants and antiplatelets in women that have suffered a stroke has been found.[334] Further research is required to identify the treatment barriers and ways to address these barriers.

11.2.1.7 Unmeasured factors

The association between sex and outcomes may be confounded by sex-specific risk factors of stroke, rehabilitation outcomes, and some cultural or social factors. These types of data were not collected in the studies included in this thesis. New population-based, purposely designed studies or re-analysis of existing studies that do gather these data are needed to understand how stroke affects women and men's health in relation to these aspects. This approach will allow us to capture a wider perspective of the disease including patient characteristics, stroke risk factors, comorbid conditions, processes of care, and long-term outcomes after stroke from different settings.

11.2.2 Broader implications of research findings

Several findings of the thesis were not related to the sex differences in outcomes, but have important implications for both men and women and are discussed below.

11.2.2.1 Both women and men with stroke had excess mortality and significant HRQoL loss compared to the general population

People with stroke had excess deaths due to stroke, other CVD, and cancer when compared to the general population. This could be explained by the fact that these causes of death share common risk factors, such as hyperlipidemia, diabetes, and smoking. Effective primary and secondary stroke prevention strategies should be developed, evaluated and implemented to ameliorate mortality risk due to stroke and other CVD. There is a need to implement more effective prevention programs for both high-risk individuals and the general population. The high-risk approach

includes identification and management of people with increased absolute risk of CVD and stroke. Preventive interventions among high-risk individuals such as pharmacological treatment have led to a significant reduction in the incidence of stroke and CVD.[431] For example, evidence has shown that the use of 'polypill' therapy that combines multiple drugs (i.e. statin, antihypertensive agents, aspirin) could reduce stroke and other CVDs by 80% among those ≥55 years with existing CVD.[364]

On the other hand, promoting prevention strategies at the population level is also important. There has been recent interest in population-wide strategies for primary stroke prevention that target people at any level of CVD risk using e-health.[432] Government investment in preventive programs is limited.[433] This suggests a need to advocate for more spending on prevention. There should also be a focus on examining the cost-effectiveness of preventive health interventions which are associated with better cardiovascular and general health.[433] According to the Danish National Patient Registry (2015), female patients usually have lower income than their male counterparts.[434] In this study, there were greater expenses due to hospitalisation and medication (direct cost) among younger adults and women with stroke whereas there was no sex difference in indirect health cost.[434] Little is known about the direct and indirect health costs associated with poorer outcomes after stroke in women compared to men,[434,435] requiring further research.

In my findings, a large proportion of deaths were attributable to cardiac disease. It is recommended in clinical stroke guidelines on ECG monitor for at least 24 hours, [355319] and 94% patients with received the cardiac functional test while in hospital, according

to the National Stroke Audit Report 2013 (Australia).[346] However, little is known about the effectiveness of routine cardiac imaging or continuous monitoring in the longer term, requiring further research.[355] More sensitive and specific biomarkers or advanced cardiac imaging (i.e. three-dimension echocardiography) may provide helpful information for better detection and management of cardiovascular health following stroke.

Cancer generally has a long development period, suggesting that deaths from cancer after stroke were mostly from pre-existing diseases. There is some discussion on screening for cancer in the patient with cryptogenic stroke that may help to diagnose occult cancer and inform future interventions, but the cost-effectiveness of this approach warrants more research.[365,366] The other potential mechanism is related to newly diagnosed cancer patients who have a stroke possibly due to hypercoagulation (i.e. causing thromboembolism)[367] or side-effects of cancer treatment.[368] Given the lack of cancer-related data in stroke studies, it may be useful to further examine the predictors of long-term outcomes among people with stroke and cancer, potentially using data linkage. Because patients with stroke and a history of cancer have an increased risk of recurrent stroke and cardiovascular mortality,[365] these outcomes should be considered in future stroke research together with other data including cancer treatment (e.g. chemotherapy, radiotherapy). Understanding the interrelationships between cancer and stroke is important given the large burden associated with these two diseases.[368]

11.2.3 More opportunities for rehabilitation programs and interventions to increase participation, particularly for women after stroke

Women have been reported to have worse functional outcome after stroke rehabilitation than men, even after matching (i.e. using propensity score matching technique) for age, stroke severity, and time to hospital admission.[247] One explanation is that existing functional limitations, that may be more common in women, can influence the choice of discharge destination (i.e. type of rehabilitation setting) and subsequent rehabilitation outcomes in women after stroke.[246] Women appear to have lower response to rehabilitation particularly on mobility than men, which might be related to sex-related differences in muscular strength.[246] Numerous factors that are associated with outcomes including social factors (e.g. sex, age, ethnicity, and culture), pre-stroke health, clinical indicators, and post-stroke conditions (e.g. living alone, social isolation) should be taken into account in rehabilitation programs.[280]

Rehabilitation following stroke is quite individualised and focused. Although in many countries (e.g. Australia, New Zealand, and United Kingdom) it is recommended that all people with stroke should receive rehabilitation, access to rehabilitation is rarely reported.[436] The proportion of people with stroke accessing in-hospital rehabilitation varied by region (i.e. from 13% in Sweden, 30% in Australia, to 57% in Israel) whereas little is known about the access to home- or community-based rehabilitation.[436] Further work is warranted to identify potential barriers to receiving rehabilitation services to understand ways to engage more people into rehabilitation. One of the strategies to boost patients' engagement in rehabilitation activities is to use advanced technology (e.g. digital game systems), which may keep stroke survivors

entertained and motivated during the therapy process.[437] The access to rehabilitation may be restricted by geographical distances or a lack of allied health professionals in rural and remote areas.[438] Stroke telerehabilitation may offer more opportunities to make rehabilitation services more convenient and accessible, particularly for those living in under-resourced areas, to improve outcomes after stroke.[438] There is some evidence of inequities in access to rehabilitation whereby clinicians tended to recommend the patients for rehabilitation based on subjective rehabilitation services selection criteria rather than patient's requirements.[439] Improvements in rehabilitation service delivery is needed to meet the rehabilitation needs of patients with stroke. [439]

Allied health with a range of services such as physiotherapy, occupational therapy, social work and speech-language therapy will help to facilitate participation after stroke. More recently, creative art therapies (i.e. music) combined with conventional physical therapy program have been suggested to further improve functional outcomes and HRQoL as well as reduce depression after stroke.[440] Also, fitness training in combination with psychosocial or educational interventions may have some benefits on improving outcomes following stroke, like the exercise-based cardiac rehabilitation has had, particularly on reducing CVD mortality.[362,363]

11.2.4 Outcome assessments in research studies

There has been increasing evidence that several clinical and social needs in survivors of stroke remain unmet long after stroke.[261,441-443] Common domains of unmet needs include activities and participation, environmental factors, body functions, acute care, and secondary prevention. However, many of these are not captured in current

research (e.g. only two out of 13 studies included in the INSTRUCT had a participation outcome).[24] More outcome assessments and examination of the reasons for unmet needs of stroke survivors in population-based studies would offer specific targets for future interventions to address any identified gaps.

The factors associated with greater unmet needs also varied by countries and study settings. Younger persons, the elderly, men, and women express different senses, perception, and coping strategies with the consequences of stroke,[444] which potentially leads to their different needs.[261,441,442] Other predictors of unmet needs at the time of stroke have been identified such as living alone (many of whom are older women),[442] ethnic minority groups,[443] living in the most deprived areas,[443] higher education,[261] atrial fibrillation,[442] diabetes,[442] previous stroke,[442] stroke severity,[442] and haemorrhages.[442] Higher levels of unmet needs were also observed among those with greater functional limitations after stroke,[261,441,442] pain,[442] depression,[261,442] the receipt of community services,[261] the inability to return to work.[441] Strategies aimed at better supporting stroke survivors and their families should be well-developed according to age, gender, and location to meet people's needs in facilitating independent living, participation and increased HRQoL.[445] The unmet needs are generally most prevalent in secondary stroke prevention,[261] meaning that the success of secondary prevention management of stroke and CVD is more likely to improve the long-term outcomes after stroke for both men and women. In Australia, websites such as "EnableMe" (at https://enableme.org.au/),[446] developed by the National Stroke Foundation, supply trusted resources on impacts of stroke to survivors and provide an important advance in meeting their needs.

11.2.5 Further work in low- and middle-income countries is needed

The data used within this thesis mostly focused on high-income countries (HICs) due to the lack of eligible studies conducted in low- and middle-income countries (LMICs).

11.2.5.1 More population-based studies

There are some 'gold standard' stroke incidence studies in LMICs that were identified in my systematic search. However, very few have data on outcomes following stroke, particularly in the long term. This situation is most likely because follow-up can be labour intensive and costly. Linkage of stroke incidence studies to the national death registrations offers a solution for the lack of long-term survival information in many HICs.[236] National registration systems for deaths, nevertheless, remain uncommon in most LMICs.[447] I strongly advocate for other researchers to conduct long term follow-up within their stroke studies, particularly in LMICs, given the importance of understanding the natural history of stroke.

The burden of stroke is considerable in LMICs accounting for 52% of prevalent strokes, 71% stroke-related deaths, and 78% of disability-adjusted life years lost, globally.[1] Developing countries are experiencing about 23% greater incidence of stroke than more developed countries, and the gap continues to widen.[1] In HICs, the burden of stroke is related to the ageing population while in LMICs, stroke occurs in younger age mostly due to the increased CVD risk factors among adults.[448] Future studies designed to investigate the patient profile and outcomes of early onset strokes, as well as any sex differences in developing countries are of utmost importance. This

extra information would establish a better understanding of how to reduce the impact of stroke in developing countries such as through developing evidence-based models of health care and policy frameworks. For instance, several groups/organisations working in the stroke field and authorities in Australia work together to tackle agreed priorities to improve care based on gaps identified in the national audit and other data sources.[324,449]

11.2.5.2 More stroke clinical registries

Although it is essential to ensure access to evidence-based care to reduce the impact of stroke, current evidence on the quality of stroke care has mostly been documented in HICs. In developed countries, given the use of effective interventions for quality improvement and the availability of specialists with extra training in neurology or stroke care, the adherence to clinical guidelines for stroke has been increased.[425-428] In contrast, there is a dearth of evidence for these type of programs, as well as lack of stroke care professionals in LMICs, suggesting further researches needed to understand and overcome these barriers.[450]

According to a recent update on global stroke statistics by Thrift and colleagues, there have been eight countries that either lack or provide outdated data on stroke incidence but have national clinical registries of hospital-based data.[58] On the one hand, population-based stroke incidence studies may not be undertaken nor repeated due to costs and labour intensity.[58] On the other hand, clinical stroke registries allow us to capture aspects of the quality of care through measuring current processes of in-hospital care as well as patient outcomes.[25] National stroke registries, therefore, could

be serve as a proxy for population-based incidence studies in locations where the majority of incidence cases are treated in hospital.[58]

It is advocacated that countries unable to afford stroke incidence studies, particularly in LMICs, should consider establishing registry program for stroke care, both on the national and regional level.[451] There is also a pressing need for quality improvement efforts[452] to monitor and improve the quality of care in both developed and developing countries.

11.2.5.3 More examination of sex differences in stroke outcome

Of a small number of stroke studies conducted in LMICs, few have been designed to investigate the sex- differences in outcomes following stroke or have not reported findings by sex categories. There are gender differences in the social determinants of health factors, and these gaps appear to be more substantial in LMICs than in HICS.[453] For example, women in LMICs, compared to men, often sleep shorter hours, spend less time on social and cultural activities but more hours on unpaid work, housework, and taking care of children and adults,[453] which may influence the recovery after stroke, community reintegration, survival and HRQoL. Therefore, these social and cultural factors need to be investigated when considering the sex differences in outcomes after stroke in LMICs.

11.2.6 Better evaluation of-pre-stroke function and patient-reported outcomes after stroke

In the previous chapters, the problems related to current measures on functional ability before stroke (i.e. using the pre-morbid mRS),[454,455] comorbidities, and patient outcomes after stroke were outlined. More reliable and sensitive stroke-assessment scales that accurately reflect pre-stroke health, stroke outcomes and patients' experience of life after stroke will allow greater opportunities for future interventions to reduce the burden of stroke for both men and women.

Because participation restriction is an important person-centred outcome after stroke but rarely assessed in stroke research,[68] this would be an important outcome to advocate for in future studies. Current participation instruments (e.g. London Handicap Scale) were designed to evaluate healthcare interventions in a population rather than individuals[257] and the assessments may reflect what people do, not what they can do.[258] New instruments to improve measurement of patient-centered outcomes particularly participation following stroke may address these problems. Some of relevant scales which measures participation include the Nottingham extended activities of daily living scale (NEADL) or the Activity Card Sort Test, used in more recent studies,[259] and international standard sets of patient-centred outcome measures (PROMS).[68]

A myriad of life perspectives following stroke may differ by sex but receive little investigation. In relation to the participation outcome, they include communication, general tasks and demands, or performing household tasks[259] while in HRQoL

outcome, these domains are vision, language, thinking, energy, and memory. In my research, post-stroke mood disorder (e.g. anxiety, depression) appeared to contribute to women's poorer HRQoL. However, whether there are differences between men and women in the diagnosis and response to post-stroke depression treatment and its association with HRQoL are uncertain. Recent international standard sets of PROMS after stroke that are valid and reliable may be helpful to further our understanding of sex differences in outcome, as well as making the data comparable between countries and care settings.[68] The PROMS categories recommended for assessment include survival, processes of care, acute complications, and patient-reported outcomes.[68] Patient-reported outcomes proposed for assessment at 3-months post-stroke are pain, mood, feeding, self-care, mobility, communication, cognitive functioning, social participation, ability to return to usual activities, and HRQoL.[68] There has been an abundance of high-quality research (i.e. randomised clinical trials, population-based studies, and clinical stroke registries) with PROMs, which provide numerous opportunities to explore the ways to improve patient-relevant outcomes after stroke.[23]

11.3 **Conclusion**

The differences between men and women in outcomes after stroke are mostly explained by age, pre-exisiting functional limitations, and stroke severity. Therefore, primary prevention of stroke and other CVD is paramount. There are more opportunities for better access to evidence-based care, as well as focused rehabilitation programs that provide more support for women, the elderly, and other vulnerable individuals. We should reassess all pre-stroke measures and stroke-assessment scales to ensure the accurate capturing of patient experience after stroke,

which would be helpful to target the interventions to reduce or postpone the devastating impact of stroke. Overall, this thesis has addressed my primary aims of understanding the magnitude of sex differences in outcomes after stroke and the causes of these differences. There do, however, remain further avenues for research and the development of interventions to mitigate differences between men and women. These will ultimately reduce the burden of stroke worldwide in men and women.

Appendix A: Sex differences in long-term mortality after stroke in the INternational STRoke oUtComes sTudy

Supplemental Table A-1a. Characteristic of included cohort studies from Oxford, Joinville, Melbourne, Arcadia and Perth by sex

	Oxford		Joinville		Melbourne		Arcadia		Perth	
Characteristic	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
SOCIODEMOGRAPHIC										
Mean (SD) Age	**71.9 (12.7)**	**77.0 (13.1)**	62.9 (13.3)	64.1 (16.5)	**72.1 (13.4)**	**76.3 (15.0)**	75.1 (11.9)	76.0 (11.3)	**72.6 (13.8)**	**77.1 (12.0)**
Race (%)										
Caucasian	-	-	88.0	92.0	92.1	94.4	-	-	-	-
Non-*Caucasian*			11.6	7.4	3.3	2.7				
Unknown			0.4	0.6	4.6	2.9				
Marital status (%)										
Single/widowed	**23.3**	**49.5**	-	-	-	-	-	-	**33.3**	**56.3**
Married	**62.3**	**36.0**							**63.2**	**38.5**
Unknown	**14.3**	**14.5**							**3.5**	**5.2**
Education level (%)										
≤ Grade 12	61.6	62.3	94.5	93.0	43.6	44.7	-	-	-	-
> Grade 12	14.6	8.9	5.1	6.8	51.5	54.3				
Unknown	23.8	28.8	0.4	0.2	5.0	1.0				
Social class (%)										
Professional	15.2	6.0	-	-	36.1	30.0	-	-	17.2	6.3
Non-manual	21.4	28.7			10.6	12.2			6.9	9.4
Manual	39.6	32.4			44.1	31.7			33.3	20.8
Unknown	23.8	32.9			9.2	26.1			42.5	63.5
PRE-STROKE HEALTH										
In an institution (%)										
Yes	-	-	-	-	**7.9**	**21.5**	-	-	8.1	18.8
No					**90.4**	**77.3**			89.7	78.1
Unknown					**1.7**	**1.2**			2.3	3.1
Modified Rankin Score (%)										
0-2	**83.5**	**70.6**	-	-	-	-	99.0	98.0	71.3	56.3
3-5	**13.2**	**26.0**					0.3	0.8	18.4	27.1
Unknown	**3.4**	**3.4**					0.7	1.2	10.3	16.7
Barthel Index score (%)										
20	-	-	-	-	**50.9**	**36.4**	-	-	**69.0**	**51.0**
<20					**11.6**	**17.1**			**20.7**	**33.3**
Unknown					**37.4**	**46.5**			**10.3**	**15.6**
Mean (SD) modified Rankin Score	**0.94 (1.18)**	**1.45 (1.31)**	-	-	-	-	0.39 (1.62)	0.44 (0.70)	1.12 (1.42)	1.54 (1.48)
Mean (SD) Barthel Index	-	-	-	-	**18.9 (3.14)**	**18.2 (4.30)**	-	-	18.7 (3.2)	17.5 (5.0)
MEDICAL HISTORY										
Hypertension (%)										
Yes	**59.2**	**63.6**	**62.7**	**68.9**	50.4	55.8	78.3	84.6	52.9	58.3
No	**40.2**	**36.4**	**37.3**	**31.1**	48.0	42.3	21.7	15.5	39.1	39.6
Unknown	**0.5**	**0.0**	**0.0**	**0.0**	1.5	1.9	0.0	0.0	8.1	2.1
Atrial fibrillation (%)										
Yes	20.1	23.0	8.9	10.6	20.7	22.6	30.7	38.2	19.5	24.0
No	79.6	76.9	91.1	89.4	77.4	74.8	69.3	61.8	73.6	70.8
Unknown	0.3	0.1	0.0	0.0	1.9	2.6	0.0	0.0	6.9	5.2
Ischaemic heart disease (%)										
Yes	**14.8**	**8.6**	**9.7**	**4.7**	**16.4**	**10.7**	18.1	15.0	17.2	6.3
No	**84.2**	**91.0**	**90.3**	**95.4**	**82.9**	**87.4**	81.9	85.0	78.2	88.5
Unknown	**1.0**	**0.4**	**0.0**	**0.0**	**0.7**	**1.9**	0.0	0.0	4.6	5.2
Peripheral vascular disease (%)										
Yes	**8.7**	**5.3**	-	-	**11.6**	**5.5**	8.7	6.5	-	-
No	**90.7**	**94.4**			**87.4**	**92.3**	91.3	93.5		
Unknown	**0.6**	**0.3**			**1.0**	**2.2**	0.0	0.0		
Transient ischaemic attack (%)										
Yes	13.9	12.1	6.3	4.0	8.4	8.2	19.1	13.4	20.7	12.5

Supplemental Table A-1a. Characteristic of included cohort studies from Oxford, Joinville, Melbourne, Arcadia and Perth by sex

	Oxford		Joinville		Melbourne		Arcadia		Perth	
Characteristic	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
No	86.0	87.8	93.7	96.0	90.6	91.0	80.9	86.6	64.4	76.0
Unknown	0.2	0.1	0.0	0.0	1.0	0.8	0.0	0.0	14.9	11.5
Diabetes (%)										
Yes	**14.9**	**11.5**	-	-	**20.0**	**14.1**	27.8	32.1	20.7	16.7
No	**84.6**	**88.5**			**79.3**	**84.8**	72.2	67.9	77.0	82.3
Unknown	**0.4**	**0.0**			**1.0**	**1.1**	0.0	0.0	2.3	1.0
Dementia (%)										
Yes	-	-	-	-	**5.3**	**13.1**	-	-	-	-
No					**73.2**	**65.8**				
Unknown					**21.5**	**21.1**				
Smoking (%)										
Current	**17.3**	**13.2**	**28.4**	**17.6**	**17.8**	**11.5**	**34.0**	**2.0**	**4.2**	**4.2**
Former	**51.3**	**27.1**	**40.6**	**18.0**	**45.1**	**18.9**	-	-	**14.6**	**14.6**
Never	**28.7**	**55.5**	**31.0**	**64.5**	**27.7**	**50.3**	**66.0**	**98.0**	**45.8**	**45.8**
Unknown	**2.8**	**4.2**	**0.0**	**0.0**	**9.4**	**19.3**	**0.0**	**0.0**	**24.1**	**35.4**
Alcohol use (%)										
Non-drinkers	**27.0**	**54.0**	**51.9**	**80.6**	**18.6**	**40.2**	**79.3**	**98.4**	**24.1**	**26.0**
Not heavy drinkers	**60.4**	**33.3**	**38.3**	**18.0**	**51.1**	**35.4**	-	-	**6.9**	**11.5**
Heavy drinkers	**3.6**	**1.6**	**9.9**	**1.5**	**8.9**	**1.1**	**20.7**	**1.6**	**34.5**	**13.5**
Ex-drinkers	-	-	-	-	**7.7**	**1.1**	-	-	**4.6**	**3.1**
Unknown	**9.0**	**11.2**	**0.0**	**0.0**	**13.7**	**22.2**	**0.0**	**0.0**	**29.9**	**45.8**
Mean (SD) Body mass index	26.3 (4.6)	25.8 (5.8)	26.4 (5.3)	26.4 (6.1)	-	-	-	-	25.2 (3.8)	24.7 (3.8)
Medication										
Antihypertensives (%)										
Yes	-	-	**59.6**	**67.0**	**49.2**	**56.0**	-	-	43.7	50.0
No			**40.4**	**33.0**	**49.7**	**42.0**			46.0	42.7
Unknown			**0.0**	**0.0**	**1.0**	**2.1**			10.3	7.3
Antiplatelets (%)										
Yes	-	-	28.8	27.5	30.3	29.4	-	-	26.4	40.6
No			71.2	72.5	68.7	68.7			71.3	54.2
Unknown			0.0	0.0	1.0	1.9			2.3	5.2
HOSPITAL ADMISSION										
Hospital admission (%)										
Yes	85.4	86.2	100.0	100.0	**93.3**	**89.7**	92.6	92.3	75.9	76.0
No	14.6	13.8	0.0	0.0	**6.7**	**10.3**	7.4	7.7	24.1	24.0
Time to arrive hospital (%)										
≤ 4.5 hours	-	-	42.0	45.0	24.5	24.2	-	-	16.7	17.8
> 4.5 – 24 hours			25.4	19.5	9.3	9.5			7.6	9.6
> 24 hours			29.6	32.4	6.6	4.3			10.6	16.4
Unknown			2.9	3.2	59.5	62.0			66.2	56.2
STROKE-RELATED FACTORS										
Stroke type (%)										
Ischaemic stroke	**82.6**	**78.1**	79.1	82.0	**74.4**	**66.5**	**68.6**	**66.3**	78.2	75.0
Intracerebral haemorrhage	**8.1**	**8.2**	11.4	4.8	**16.1**	**13.3**	**14.6**	**8.5**	11.5	9.4
Subarachnoid haemorrhage	**2.4**	**5.7**	4.9	6.1	**2.7**	**7.1**	**1.6**	**3.3**	5.8	6.3
Undetermined	**6.9**	**8.0**	4.5	5.1	**6.8**	**13.1**	**15.2**	**22.0**	4.6	9.4
Stroke severity										
Mean (SD) NIHSS	**5.2 (6.6)**	**6.6 (7.5)**	7.2 (7.8)	8.0 (8.5)	**8.1 (8.5)**	**9.9 (9.5)**	-	-	8.3 (8.3)	9.3 (8.6)
Mean (SD) GCS, reversed	-	-	-	-	-	-	**4.8 (3.7)**	**5.5 (3.5)**	-	-
Loss of consciousness (%)										
Yes	-	-	-	-	**20.5**	**27.6**	11.7	14.6	-	-
No					**57.8**	**51.4**	80.9	77.6		
Unknown					**21.7**	**20.9**	7.4	7.7		
Body paralysis (%)										
Yes	-	-	-	-	31.1	33.3	33.3	33.7	-	-
No					4.6	59.2	59.2	58.4		
Unknown					21.3	7.4	7.4	7.7		
Incontinence (%)										
Yes	-	-	-	-	**15.7**	**21.3**	15.9	20.7	-	-
No					**78.8**	**73.9**	76.7	71.5		
Unknown					**5.5**	**4.8**	7.4	7.7		
POST-STROKE FACTORS										
Depression at 1 year†										
Yes	-	-	-	-	43.1	35.5	-	-	-	-

Supplemental Table A-1a. Characteristic of included cohort studies from Oxford, Joinville, Melbourne, Arcadia and Perth by sex

	Oxford		Joinville		Melbourne		Arcadia		Perth	
Characteristic	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
No					9.6	9.2				
Unknown					47.3	55.4				
Depression at 5 years†										
Yes	-	-	-	-	9.5	10.8	-	-	-	-
No					59.3	56.9				
Unknown					31.2	32.3				
Recurrence at 1 year										
Yes	8.7	10.8	-	-	0.5	0.8	4.9	4.5	-	-
No	91.3	89.2			99.5	99.2	92.9	89.8		
Unknown	0.0	0.0			0.0	0.0	2.3	5.7		
Recurrence at 5 years										
Yes	7.1	11.8	-	-	7.0	6.8	-	-	-	-
No	46.7	45.1			93.0	93.2				
Unknown	46.2	43.2			0.0	0.0				

Bold denotes statistically significant results, NIHSS, National Institutes of Health Stroke Scale, GCS, Glasgow Coma Scale.

* among hospitalised patients; † among survivors

Supplemental Table A-1b. Characteristic of included cohort studies from Orebro, Dijon, Martinique, and Porto by sex

	Orebro		Dijon		Martinique		Porto	
Characteristic	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
SOCIODEMOGRAPHIC								
Mean (SD) Age	**73.9 (10.7)**	**78.9 (10.7)**	**71.4 (14.1)**	**76.4 (15.4)**	**67.9 (14.4)**	**74.5 (14.3)**	**68.7 (12.0)**	**72.6 (13.5)**
Marital status (%)								
Single/widowed	**36.1**	**66.8**	-	-	-	-	-	-
Married	**63.9**	**31.7**						
Unknown	**0.0**	**1.4**						
Education level (%)								
≤ Grade 12	-	-	-	-	-	-	75.4	63.1
> Grade 12							3.2	1.5
Unknown							21.5	35.4
Social class (%)								
Employed	-	-	-	-	29.5	19.3	21.5	10.2
Retired					62.1	64.1	72.2	72.3
Unemployed & other					8.4	16.6	1.4	8.7
Unknown					0.0	0.0	4.9	8.9
PRE-STROKE HEALTH								
In an institution (%)								
Yes	**7.1**	**17.3**	**3.6**	**10.7**	-	-	-	-
No	**92.9**	**82.7**	**96.5**	**89.3**				
Unknown	**0.0**	**0.0**	**0.0**	**0.0**				
Modified Rankin score (%)								
0-2	-	-	-	-	-	-	**90.5**	**77.7**
3-5							**7.4**	**14.4**
Unknown							**2.1**	**7.9**
Barthel Index score (%)								
20	**67.5**	**54.3**	-	-	-	-	-	-
<20	**5.9**	**7.2**						
Unknown	**26.6**	**38.5**						
Mean (SD) modified Rankin score	-	-	-	-	-	-	**0.54 (1.03)**	**0.99 (1.30)**
Mean (SD) Barthel Index	19.6 (1.4)	19.2 (2.9)	-	-	-	-	-	-
MEDICAL HISTORY								
Hypertension (%)								
Yes	29.0	38.5	66.3	65.2	**63.9**	**74.2**	56.7	63.9
No	67.5	57.7	32.7	33.7	**34.7**	**23.4**	43.3	36.1
Unknown	3.6	3.9	1.0	1.1	**1.4**	**2.4**	0.0	0.0
Atrial fibrillation (%)								
Yes	23.1	24.5	**19.1**	**25.0**	12.3	14.6	10.9	15.6
No	79.9	75.5	**79.8**	**73.8**	86.3	83.1	89.1	84.4
Unknown	0.0	0.0	**1.1**	**1.2**	1.4	2.4	0.0	0.0
Ischaemic heart disease (%)								
Yes	16.6	12.0	**20.1**	**16.1**	4.6	6.8	7.4	9.9
No	83.4	88.0	**78.7**	**82.7**	94.0	90.9	92.6	90.1
Unknown	0.0	0.0	**0.97**	**1.3**	1.4	2.4	0.0	0.0
Peripheral vascular disease (%)								
Yes	**36.1**	**24.0**	**11.8**	**6.4**	**9.5**	**16.6**	**7.4**	**3.7**
No	**62.7**	**74.5**	**87.2**	**92.4**	**89.1**	**81.0**	**84.2**	**77.0**
Unknown	**1.2**	**1.4**	**1.0**	**1.2**	**1.4**	**2.4**	**8.5**	**19.3**
Transient ischaemic attack (%)								
Yes	16.0	13.5	11.2	10.4	4.2	6.1	9.9	7.7
No	84.0	86.5	88.8	89.6	55.1	51.9	90.1	92.3
Unknown	0.0	0.0	0.0	0.0	40.7	42.0	0.0	0.0
Diabetes (%)								
Yes	20.1	15.9	-	-	-	-	-	-
No	78.1	80.8						
Unknown	1.8	3.4						
Dementia (%)								
Yes	7.1	15.9	-	-	-	-	-	-
No	92.9	84.1						
Unknown	0.0	0.0						
Smoking (%)								
Current	**26.0**	**14.9**	**42.3**	**9.3**	**14.0**	**0.0**	**28.9**	**3.5**
Former	**-**	**-**	**9.1**	**1.3**	**-**	**-**	**16.9**	**0.5**
Never	**62.7**	**77.9**	**36.9**	**74.5**	**84.6**	**97.6**	**54.2**	**96.0**
Unknown	**11.2**	**7.2**	**11.7**	**15.0**	**1.4**	**2.4**	**0.0**	**0.0**

Supplemental Table A-1b. Characteristic of included cohort studies from Orebro, Dijon, Martinique, and Porto by sex

	Orebro		Dijon		Martinique		Porto	
Characteristic	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Alcohol use (%)								
Non-drinkers	-	-	**88.5**	**96.5**	**73.7**	**93.6**	**28.5**	**57.7**
Current drinkers*			**10.0**	**2.0**	**24.9**	**4.1**	**60.6**	**18.3**
Ex-drinkers			-	-	-	-	-	-
Unknown			**1.6**	**1.6**	**1.4**	**2.4**	**10.9**	**24.0**
Mean (SD) Body mass index	-	-	-	-	-	-	26.3 (3.6)	26.5 (5.2)
HOSPITAL ADMISSION								
Hospital admission (%)								
Yes	92.9	91.4	99.8	99.8	93.7	93.2	95.8	95.1
No	7.1	8.7	0.2	0.2	6.3	6.8	4.2	5.0
Time to arrive hospital† (%)								
≤ 4.5 hours	-	-	-	-			4.4	39.6
> 4.5 – 24 hours					86.5	82.6	30.2	35.9
> 24 hours					13.5	17.1	17.3	12.5
Unknown					0.0	0.4	9.2	12.0
STROKE-RELATED FACTORS								
Stroke type (%)								
Ischaemic stroke	**74.0**	**71.6**	83.1	82.3	**75.1**	**78.0**	77.1	75.5
Intracerebral haemorrhage	**14.8**	**9.1**	11.9	11.3	**16.1**	**9.5**	16.6	15.8
Subarachnoid haemorrhage	-	-	2.9	3.5	**3.5**	**3.4**	1.8	4.5
Undetermined	**11.2**	**19.2**	2.2	2.9	**5.3**	**9.2**	4.6	4.2
Stroke severity								
Mean (SD) NIHSS	8.2 (8.8)	10.0 (9.7)	**7.2 (7.1)‡**	**8.2 (7.9)‡**	-	-	-	-
Mean (SD) UNSS, reversed	-	-	-	-	-	-	**9.3 (9.2)**	**12.3 (10.5)**
Loss of consciousness (%)								
Yes	-	-	**20.8**	**25.3**	-	-	3.9	7.2
No			**79.2**	**74.8**			96.1	92.8
Unknown			**0.0**	**0.0**			0.0	0.0
Body paralysis (%)								
Yes	-	-	**71.9**	**73.1**	-	-	70.4	31.4
No			**27.0**	**26.5**			29.6	68.6
Unknown			**1.1**	**0.5**			0.0	0.0
Barthel Index score at onset (%)								
> 60	-	-	-	-	45.3	35.9	-	-
≤ 60					24.6	30.9		
Unknown					30.2	33.2		
POST-STROKE FACTORS								
Depression at 5 years§	-	-	-	-	10.7	12.2	-	-
Yes					89.3	87.8		
No					0.0	0.0		
Unknown								
Recurrence at 1 year§								
Yes	-	-	3.7	8.8	4.9	8.2	9.9	
No			96.3	91.2	95.1	91.8	90.1	
Unknown			0.0	0.0	0.0	0.0	0.0	0.0
Recurrence at 5 years§								
Yes	-	-	8.3	8.2	-	-	18.7	14.4
No			91.7	91.9			81.3	85.6
Unknown			0.0	0.0			0.0	0.0

Bold denotes statistically significant results, NIHSS, National Institutes of Health Stroke Scale, UNSS, Unified Neurological Stroke Scale.

*current drinker = not heavy drinkers and heavy drinkers; † among hospitalised patients; ‡ NIHSS had been measured since the year '08 (n=1552) in the study from Dijon ('87-2013); § among survivors

Supplemental Table A-1c. Characteristic of included cohort studies from Auckland, L'Aquila, Matão, and Tartu by sex

	Auckland		L'Aquila		Matão		Tartu	
Characteristic	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
SOCIODEMOGRAPHIC								
Mean (SD) Age	**68.7 (13.7)**	**74.5 (14.3)**	**72.6 (11.9)**	**76.6 (10.7)**	65.1 (11.6)	65.3 (12.2)	**67.8 (12.2)**	**75.0 (11.2)**
Race (%)								
Caucasian	-	-	-	-	80.4	80.0	-	-
Non-*Caucasian*					13.7	10.0		
Unknown					5.9	10.0		
Marital status (%)								
Single/widowed	**32.5**	**62.0**	-	-	25.5	40.0	-	-
Married	**65.2**	**34.1**			68.6	56.7		
Unknown	**2.3**	**3.8**			5.9	3.3		
Education level (%)								
≤ Grade 12	38.4	49.3	-	-	78.4	90.0	-	-
> Grade 12	36.3	23.0			9.8	3.3		
Unknown	25.3	27.7			11.8	6.7		
Social class (%)								
Professional	23.1	11.5	-	-	-	-	-	-
Non-manual	15.6	22.4						
Manual	40.8	17.7						
Unknown	20.5	48.4						
PRE-STROKE HEALTH								
Pre-stroke dependence (%)								
Yes	**8.9**	**22.0**	-	-	-	-	-	-
No	**87.6**	**74.1**						
Unknown	**3.6**	**4.0**						
Modified Rankin score (%)								
0-2	-	-	-	-	-	-	90.5	77.7
3-5							7.4	14.4
Unknown							2.1	7.9
Mean (SD) modified Rankin score	-	-	-	-	-	-	**0.89 (0.95)**	**1.09 (0.92)**
MEDICAL HISTORY								
Hypertension (%)								
Yes	**50.1**	**56.9**	**60.9**	**69.2**	64.7	70.0	**54.8**	**66.0**
No	**45.6**	**39.0**	**38.3**	**23.7**	29.4	26.7	**45.2**	**34.0**
Unknown	**4.4**	**4.1**	**0.8**	**1.1**	5.9	3.3	**0.0**	**0.0**
Atrial fibrillation (%)								
Yes	**17.5**	**23.2**	**18.0**	**25.1**	2.0	0.0	25.4	32.8
No	**80.4**	**74.5**	**80.1**	**71.8**	90.2	96.7	74.6	67.2
Unknown	**2.1**	**2.4**	**2.0**	**3.1**	7.8	3.3	0.0	0.0
Ischaemic heart disease (%)								
Yes	**23.4**	**18.1**	**24.8**	**24.3**	3.9	10.0	33.9	38.7
No	**75.6**	**80.4**	**72.9**	**72.1**	88.2	86.7	66.1	61.3
Unknown	**1.1**	**1.5**	**2.2**	**3.6**	7.8	3.3	0.0	0.0
Peripheral vascular disease (%)								
Yes	-	-	**11.4**	**12.0**	2.0	10.0	-	-
No			**86.5**	**83.7**	90.2	86.7		
Unknown			**2.1**	**4.3**	7.8	3.3		
Transient ischaemic attack (%)								
Yes	-	-	7.4	7.5	7.8	3.3	5.1	5.9
No			88.4	87.6	84.3	93.3	94.9	94.1
Unknown			4.2	4.9	7.8	3.3	0.0	0.0
Dementia (%)								
Yes	1.7	1.1	-	-	2.0	6.7	-	-
No	97.3	97.4			90.2	90.0		
Unknown	1.1	1.6			7.8	3.3		
Smoking (%)								
Current	**16.2**	**11.8**	**45.3**	**4.2**	43.1	20.0	-	-
Former	**49.9**	**29.2**	-	-	-	-		
Never	**26.7**	**47.0**	**44.7**	**83.1**	51.0	76.7		
Unknown	**7.2**	**12.0**	**10.1**	**12.7**	5.9	3.3		
Alcohol use (%)								
Non-drinkers	**57.7**	**42.9**	-	-	**70.6**	**93.3**	-	-
Current drinkers *	**18.3**	**30.0**			**21.6**	**3.3**		
Ex-drinkers	**24.0**	**12.3**			-	-		
Unknown	**12.0**	**14.8**			**7.8**	**3.3**		

Supplemental Table A-1c. Characteristic of included cohort studies from Auckland, L'Aquila, Matão, and Tartu by sex

	Auckland		L'Aquila		Matão		Tartu	
Characteristic	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Mean (SD) Body mass index	**26.3 (5.7)**	**25.3 (6.4)**	-	-	-	-	-	-
Medication								
Antihypertensives (%)								
Yes	39.3	44.3	-	-	-	-	**34.5**	**49.2**
No	5.3	6.2					**45.8**	**32.4**
Unknown	55.5	49.5					**19.8**	**18.4**
Antiplatelets (%)								
Yes	35.8	38.4	-	-	-	-	17.0	21.5
No	60.7	57.7					62.7	53.9
Unknown	3.5	4.0					20.3	24.6
HOSPITAL ADMISSION								
Hospital admission (%)								
Yes	**95.4**	**90.5**	**95.6**	**93.1**	100.0	100.0	88.1	87.5
No	**4.7**	**9.5**	**4.4**	**6.9**	0.0	0.0	11.9	12.5
Time to arrive hospital† (%)								
≤ 4.5 hours	-	-	-	-	-	-	34.0	33.9
> 4.5 – 24 hours	80.7	80.9					5.8	4.0
> 24 hours	12.0	12.6					2.6	2.2
Unknown	7.4	6.6					57.7	59.8
STROKE-RELATED FACTORS								
Stroke type (%)								
Ischaemic stroke	**76.2**	**69.3**	83.0	82.2	82.3	86.7	77.4	76.2
Intracerebral haemorrhage	**12.0**	**12.8**	12.1	13.1	15.7	13.3	15.8	11.3
Subarachnoid haemorrhage	**6.2**	**6.1**	2.7	2.7	2.0	0.0	-	-
Undetermined	**5.7**	**11.8**	2.2	2.0	0.0	0.0	6.8	12.5
Stroke severity								
Mean (SD) NIHSS	-	-	-	-	9.2 (8.7)	11.5 (9.2)	9.1 (8.7) ‡	10.6 (8.3) ‡
Mean (SD) GCS, reversed	**2.5 (3.1)**	**3.0 (3.4)**	-	-	2.6 (3.1)	2.5 (2.4)	-	-
Loss of consciousness (%)								
Yes	**36.7**	**40.7**	31.2	32.7	-	-	-	-
No	**61.5**	**55.2**	66.4	63.9				
Unknown	**1.8**	**4.1**	2.4	3.4				
Body paralysis (%)								
Yes	84.7	84.3	**79.0**	**79.1**	-	-	-	-
No	13.5	13.4	**17.5**	**15.8**				
Unknown	1.8	2.4	**3.5**	**5.1**				
POST-STROKE FACTORS								
Depression at 5 years§								
Yes	12.9	10.7	-	-	-	-	-	-
No	19.4	17.4						
Unknown	67.7	72.0						
Recurrence at 1 year§								
Yes	-	-	7.1	7.1	15.7	10.0	-	-
No			92.9	92.9	80.4	90.0		
Unknown			0.0	0.0	3.9	0.0		

Bold denotes statistically significant results. NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.

* current drinker including not heavy drinkers and heavy drinkers; † among hospitalised patients; ‡ NIHSS scores were mapped from Scandinavian stroke scale

§ among survivors

Supplemental Table A-2. List of covariates not meeting the criteria for factors confounding the difference in 1-year mortality between women and men

Study	Covariates not meeting the criteria for confounding factors in univariable model	Confounding factors in univariable model that were not significant in the final multivariable model
Oxford	SEP, education, hypertension, AF, IHD, PVD, TIA, diabetes, BMI, smoking, hospital admission, recurrence	Marital status, alcohol
Joinville	Race, hypertension, AF, PVD, TIA, BMI, smoking, hospital admission (100%), pre-stroke medication (antihypertensives, antiplatelets, anticoagulants), delay to hospital	IHD, alcohol
Melbourne	Race, SEP, education, hypertension, IHD, PVD, TIA, diabetes, smoking, alcohol, hospital admission, recurrence, pre-stroke medication (antiplatelets, anticoagulants)	Dementia, institutional residence, onset hemiplegia, onset incontinence, onset LOC, pre-stroke antihypertensives
Arcadia	hypertension, IHD, PVD, TIA, diabetes, BMI, smoking, alcohol, stroke type, hospital admission, recurrence	Onset hemiplegia, onset incontinence, onset LOC
Perth	SEP, hypertension, AF, IHD, TIA, diabetes, smoking, alcohol, delay to hospital, pre-stroke medication (antihypertensives, antiplatelets)	Institutional residence, pre-stroke Barthel, hospital admission
Orebro	Hypertension, AF, IHD, PVD, TIA, diabetes, pre-stroke Barthel	Marital status, dementia, hospital admission, smoking
Dijon	Hypertension, IHD, PVD, TIA, alcohol, stroke severity (NIHSS), stroke type, hospital admission, onset hemiplegia, recurrence	Institutional residence
Martinique	Hypertension, AF, IHD, TIA, BMI, smoking, alcohol, stroke type, hospital admission, delay to hospital	-
Porto	Education, hypertension, AF, IHD, PVD, TIA, BMI, stroke type, stroke severity (UNSS), hospital admission, delay to hospital, onset hemiplegia, recurrence	SEP, alcohol
Auckland	SEP, education, hypertension, IHD, dementia, BMI, smoking, alcohol, pre-stroke medication (antihypertensives, antiplatelets, anticoagulants), hospital admission, delay to hospital, onset hemiplegia	Marital status, onset LOC
L'Aquila	Hypertension, IHD, PVD, TIA, onset hemiplegia, onset LOC*, recurrence	-
Matão	Race, marital status, education, age†, hypertension, AF, IHD, PVD, TIA, smoking, alcohol, hospital admission, recurrence	-
Tartu	Hypertension, AF, IHD, TIA, hospital admission, stroke type, delay to hospital, pre-stroke medication (antihypertensives, antiplatelets)	-

AF, Atrial fibrillation; BMI, body mass index; GCS, Glasgow Coma Scale; IHD, ischaemic heart disease; LOC, loss of consciousness (at onset); mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease, TIA, transient ischaemic attack; UNSS, Unified Neurological Stroke Scale; SEP, socioeconomic position.
* Not a confounder but to be included in the final multivariable model

Supplemental Table A-3. Mortality rate ratio between women and men at 1 year after stroke in crude models and models with adjustment for age, severity, atrial fibrillation and pre-stroke dependency

Study	N*	Unadjusted		Adjusted for age			Adjusted for severity			Adjusted for AF			Adjusted for pre-stroke dependency		
		MRR	(95% CI)	MRR	(95% CI)	% change†	MRR	(95% CI)	% change†	MRR	(95% CI)	% change†	MRR	(95% CI)	% change†
Oxford	1290	**1.65**	**(1.30-2.09)**	1.20	(0.93-1.53)	64%	1.26	(0.96-1.66)	53%	**1.64**	**(1.29-2.09)**	1%	**1.29**	**(1.00-1.65)**	55%
Joinville	979	**1.25**	**(0.92-1.70)**	1.13	(0.82-1.54)	46%	1.27	(0.87-1.83)	-10%	1.25	(0.92-1.70)	0%	-		
Melbourne	975	**1.42**	**(1.10-1.84)**	1.10	(0.84-1.44)	73%	1.14	(0.77-1.68)	64%	**1.36**	**(1.05-1.76)**	13%	1.18	(0.90-1.55)	53%
Arcadia	547	1.21	(0.89-0.63)	1.17	(0.87-1.58)	20%	0.85	(0.58-1.27)	184%	1.17	(0.86-1.57)	18%	-		
Perth	183	0.88	(0.51-1.54)	0.77	(0.43-1.36)	-115%	0.81	(0.43-1.50)	-75%	0.88	(0.50-1.53)	-6%	0.75	(0.41-1.37)	-132%
Orebro	377	**1.63**	**(1.09-2.46)**	1.26	(0.83-1.94)	52%	1.47	(0.79-2.73)	22%	**1.64**	**(1.09-2.49)**	-1%	1.23	(0.78-1.94)	58%
Dijon	3994	**1.21**	**(1.06-1.39)**	0.90	(0.78-1.04)	154%	1.12	(0.97-1.30)	41%	**1.16**	**(1.01-1.32)**	24%	1.13	(0.99-1.30)	24%
Martinique	569	**1.65**	**(1.19-2.29)**	**1.40**	**(1.00-1.94)**	34%	1.53	(1.07-2.18)	16%	**1.64**	**(1.18-2.28)**	2%	-		
Porto	650	1.41	(1.00-1.98)	1.16	(0.82-1.64)	57%	1.07	(0.73-1.56)	81%	1.41	(1.00-1.98)	1%	1.19	(0.84-1.70)	49%
Auckland	1177	**1.43**	**(1.12-1.44)**	1.12	(0.87-1.44)	69%	1.35	(0.96-1.88)	17%	**1.37**	**(1.08-1.77)**	11%	1.16	(0.90-1.50)	59%
L'Aquila	3794	**1.23**	**(1.09-1.39)**	1.02	(0.90-1.39)	92%	**1.24**	**(1.09-1.41)**	-2%	**1.17**	**(1.04-1.33)**	24%	-		
Matão	79	0.64	(0.24-1.69)	0.63	(0.24-1.69)	1%	0.43	(0.16-1.19)	32%	0.62	(0.24-1.64)	3%	-		
Tartu	358	**1.62**	**(1.11-2.36)**	1.16	(0.77-1.75)	69%	**1.52**	**(1.01-2.28)**	13%	**1.52**	**(1.04-1.23)**	13%	-		
Pooled	14,972	**1.35**	**(1.24-1.47)**	**1.07**	**(0.98-1.15)**	77%	**1.19**	**(1.09-1.31)**	42%	**1.33**	**(1.20-1.47)**	5%	**1.18**	**(1.06-1.32)**	45%
		I^2=26.5%	p=0.117	I^2=12.7%	p=0.317		I^2=15.5%	p=0.288		I^2=57.8%	p=0.005		I^2=66.1%	p<0.001	

Bold denotes statistically significant results; CI indicates confidence interval; MRR, rate ratio; AF, atrial fibrillation.

* the sample size were the same among the unadjusted model, age-adjusted model, and fully adjusted model

† % change of coefficient of sex difference in mortality rate ratio which was calculated by the formula (unadjusted β – adjusted β)/ unadjusted β *100

Supplemental Table A-4. List of covariates not meeting the criteria for factors confounding the difference in 5-year mortality between women and men

Study	Covariates not meeting the criteria for confounding factors in univariable model	Confounding factors in univariable model that were not significant in the final multivariable model
Oxford	SEP, education, hypertension, IHD, PVD, TIA, diabetes, BMI, smoking, hospital admission, recurrence	Marital status, alcohol
Melbourne	Race, SEP, education, hypertension, AF, IHD, PVD, TIA, diabetes, smoking, alcohol, hospital admission, recurrence, pre-stroke medication (pre-stroke antihypertensives, antiplatelets, anticoagulants)	Dementia, institutional residence, onset hemiplegia, onset incontinence, onset LOC
Orebro	Hypertension, AF, IHD, PVD, TIA, diabetes, pre-stroke Barthel	Marital status, dementia, hospital admission, smoking
Dijon	Hypertension, IHD, PVD, TIA, alcohol, stroke severity (NIHSS), stroke type, hospital admission, onset hemiplegia, recurrence	Institutional residence
Martinique	Hypertension, AF, IHD, PVD, TIA, BMI, smoking, alcohol, stroke type, hospital admission, delay to hospital	-
Porto	SEP, education, hypertension, AF, IHD, PVD, TIA, BMI, stroke type, stroke severity (UNSS), hospital admission, delay to hospital, onset hemiplegia, recurrence	Alcohol
Auckland	SEP, education, hypertension, IHD, dementia, BMI, alcohol, pre-stroke medication (antihypertensives, antiplatelets, anticoagulants), hospital admission, delay to hospital, onset hemiplegia	Marital status, onset LOC, smoking
L'Aquila	Hypertension, IHD, PVD, TIA, onset hemiplegia, onset LOC*, recurrence	-

AF, Atrial fibrillation; BMI, body mass index; GCS, Glasgow Coma Scale; IHD, ischaemic heart disease; LOC, loss of consciousness (at onset); mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease, TIA, transient ischaemic attack; UNSS, Unified Neurological Stroke Scale; SEP, socioeconomic position.
* not a confounder but to be included in the final multivariable model

Supplemental Table A-5. Mortality rate ratio between women and men at 5 years after stroke in crude models and models with adjustment for age, severity, atrial fibrillation and pre-stroke dependency

Study	N*	Unadjusted		Adjusted for age			Adjusted for severity			Adjusted for AF			Adjusted for pre-stroke dependency		
		MRR	**(95% CI)**	**MRR**	**(95% CI)**	**% change†**	**MRR**	**(95% CI)**	**% change†**	**MRR**	**(95% CI)**	**% change†**	**MRR**	**(95% CI)**	**% change†**
Oxford	732	1.24	(0.98-1.58)	0.96	(0.74-1.23)	121%	1.02	(0.67-1.54)	92%	1.28	(1.00-1.64)	-14%	1.03	(0.80-1.34)	85%
Melbourne	975	**1.34**	**(1.09-1.64)**	1.03	(0.82-1.28)	91%	1.09	(0.81-1.47)	70%	1.29	(1.04-1.59)	14%	1.14	(0.91-1.42)	56%
Orebro	377	1.57	(1.14-2.15)	1.18	(0.84-1.64)	64%	1.45	(0.94-2.24)	17%	1.57	(1.13-2.17)	0%	1.27	(0.91-1.78)	47%
Dijon	3094	1.09	(0.97-1.22)	**0.80**	**(0.71-0.90)**	360%	1.03	(0.91-1.17)	66%	1.04	(0.92-1.17)	54%	1.02	(0.91-1.15)	77%
Martinique	569	1.52	(1.17-1.97)	1.26	(0.97-1.63)	46%	1.35	(1.04-1.76)	29%	**1.51**	**(1.17-1.97)**	1%	-		
Porto	650	1.09	(0.85-1.40)	0.87	(0.67-1.14)	253%	0.92	(0.70-1.21)	194%	1.07	(0.83-1.39)	18%	0.96	(0.73-1.25)	152%
Auckland	1177	**1.45**	**(1.16-1.81)**	1.09	(0.86-1.39)	76%	**1.39**	**(1.02-1.91)**	10%	**1.38**	**(1.10-1.74)**	13%	1.13	(0.89-1.45)	66%
L'Aquila	3794	**1.09**	**(0.98-1.20)**	**0.88**	**(0.80-0.97)**	248%	**1.09**	**(0.99-1.20)**	-5%	**1.04**	**(0.94-1.14)**	59%	-		
Pooled	11368	**1.24**	**(1.12-1.38)**	0.96	(0.86-1.07)	119%	**1.11**	**(1.01-1.20)**	51%	**1.21**	**(1.08-1.36)**	11%	**1.10**	**(1.02-1.19)**	55%
		I^2=57.2%	p=0.022	I^2=59.7%	p=0.015		I^2=62.9%	p=0.009		I^2=20.9%	p=0.264		I^2=26.8%	P=0.215	

Bold denotes statistically significant results; MRR (95% CI), Mortality rate ratio (95% confidence interval); AF, atrial fibrillation.

* the sample size were the same among the unadjusted model, age-adjusted model, and fully adjusted model

† % change of coefficient of sex difference in mortality rate ratio which was calculated by the formula (unadjusted β – adjusted β)/ unadjusted β *100

Supplemental Table A-6. Analyses of heterogeneity in sex difference in mortality at 5 years after stroke among 8 population-based studies

Variables of interest		No of studies	No of death (n/N)		Unadjusted				Adjusted*			
			Men	Women	I^2 (%)	P^H	MRR(95% CI)	$P^{sub\text{-}group}$	I^2 (%)	P^H	MRR(95% CI)	$P^{sub\text{-}group}$
Study-level characteristics†												
Geographic region	Australasia	2	508/1252	758/1487	0.0	0.614	1.39 (1.19-1.61)	0.080	0.0	0.835	0.71 (0.56-0.91)	0.308
	Europe	5	2306/4596	2832/5301	29.8	0.223	1.13 (1.04-1.24)		77.1	0.002	0.73 (0.59-0.89)	
	Caribbean	1	135/285	180/295	NA	1.000	1.52 (1.17-1.97)		NA	1.000	1.16 (0.82-1.64)	
Income group	HIC	7	2814/5848	3590/6788	51.7	0.053	1.21 (1.09-1.34)	0.239	67.2	0.006	0.73 (0.62-0.85)	0.114
	LMIC | |	1	135/285	180/295	NA	1.000	1.52 (1.17-1.97)		NA	1.000	1.16 (0.82-1.64)	
Person-years	Actual	6	1230/2334	1476/2599	49.5	0.078	1.25 (1.11-1.41)	0.841	32.2	0.195	0.68 (0.59-0.79)	0.051
	Estimated	2	1719/3799	2294/4484	81.9	0.019	1.26 (0.91-1.74)		52.0	0.149	0.96 (0.75-1.22)	
Death Registries	Yes	4	1367/2848	1760/3324	56.7	0.055	1.29 (1.12-1.48)	0.501	8.9	0.349	0.72 (0.62-0.83)	0.700
	No	4	1585/3285	2010/3759	64.4	0.060	1.19 (0.98-1.44)		79.9	0.002	0.79 (0.59-1.05)	
Age difference§	≤ 4.5 years	1	1095/2049	1296/2304	NA	1.000	1.09 (0.98-1.20)	0.261	NA	1.000	0.88 (0.80-0.98)	0.474
	> 4.5 years	7	1854/4084	2474/4779	52.7	0.048	1.28 (1.14-1.45)		60.4	0.019	0.73 (0.61-0.88)	
Severity instrument	NIHSS	3	539/1118	761/1335	0.0	0.518	1.35 (1.17-1.55)	0.117	39.2	0.193	0.73 (0.56-0.96)	0.307
	Barthel	1	135/285	180/295	NA	1.000	1.52 (1.17-1.97)		NA	1.000	1.16 (0.82-1.64)	
	Others#	4	2275/4730	2829/5453	46.6	0.132	1.14 (1.02-1.26)		78.6	0.003	0.72 (0.58-0.89)	
SAH data	Yes	7	2863/5964	3637/6875	54.0	0.042	1.21 (1.10-1.34)	0.247	72.2	0.001	0.74 (0.62-0.88)	0.370
	No	1	86/169	133/208	NA	1.000	1.57 (1.14-2.15)		NA	1.000	1.01 (0.65-1.57)	
Sample size	≤1000	3	358/738	523/907	54.4	0.111	1.36 (1.08-1.72)	0.347	85.2	0.001	0.83 (0.48-1.43)	0.614
	>1000	5	2591/5395	3247/6176	53.6	0.071	1.19 (1.07-1.33)		56.1	0.058	0.75 (0.65-0.87)	
Participant-level characteristics‡												
Stroke type	IS	8	226/4949	2782/5546	35.3	0.147	1.21 (1.11-1.32)	Ref	48.7	0.058	0.88 (0.82-0.94)	Ref
	ICH	8	450/770	526/840	61.1	0.012	1.27 (0.94-1.70)	0.529	63.4	0.008	1.01 (0.85-1.19)	0.722
	SAH	7	77/186	125/279	25.1	0.237	1.14 (0.73-1.76)	0.873	56.3	0.033	1.04 (0.68-1.57)	0.746
	Undetermined	8	158/228	337/418	35.8	0.143	1.51 (1.05-2.16)	0.397	45.2	0.078	1.02 (0.77-1.35)	0.150
Age group	≤65	8	394/1605	242/1131	41.9	0.099	0.90 (0.70-1.15)	Ref	-			
	>65-75	8	1939/3786	2084/4188	33.7	0.159	0.98 (0.89-1.08)	0.917	-			
	>75	8	616/742	1444/1764	36.9	0.134	1.09 (0.90-1.30)	0.055	-			

P^H, P-value of heterogeneity; $P^{sub\text{-}group}$, P-value for subgroup analysis; Ref, reference group; NA, not applicable; IS, Ischaemic stroke; ICH, Intracerebral haemorrhage; SAH, Subarachnoid haemorrhage; Barthel, Barthel index (at onset), NIHSS, National Institutes of Health Stroke Scale; MRR (95% CI), Mortality rate ratio (95% confidence interval) between women and men; HIC, High-income country; LMIC, Low- and middle-income country.

* MRR adjusted for actual confounders, but estimates for stroke type adjusted for age only.

† Estimates were performed using two-stage method analysis

‡ estimates were performed using multivariate random-effect meta-analyses

§ indicates difference in median age at onset between women and men

| | low- and middle-income country (LMIC) group included studies conducted in Martinique

Other instruments including Glasgow coma scale and loss of consciousness

Supplemental Table A-7a. Loss to follow-up and missing data among the 13 included studies

Study	1-year				5-year			
	Data available (n)	Lost to follow-up (%)	Assess in full model (n)	Missing confounder data (%)	Data available (n)	Lost to follow-up (%)	Assess in full model (n)	Missing confounder data (%)
Oxford	1374	0.0*	1290	6.1%	760	0.0*	732	3.7%
Joinville	980	0.0	979	0.1%				
Melbourne	1316	0.0*	975	26.0%	1316	0.0	975	25.9%
Arcadia	548	1.3	547	0.2%				
Perth	183	0.0*	183	0.0%				
Orebro	377	0.0*	377	0.0%	377	0.0*	377	0.0%
Dijon	4621	0.0*	3994	13.5%	3719	0.0*	3094	16.8%
Martinique	580	0.0	569	1.9%	580	0.0	569	1.9%
Porto	688	1.3	650	5.5%	688	1.3	650	5.5%
Auckland	1423	8.2	1177	17.3%	1423	16.7	1177	17.3%
L'Aquila	4353	1.2	3794	12.8%	4353	1.2	3794	12.8%
Matão	81	0.0*	79	2.5%				
Tartu	433	0.0*	358	17.3%				
Total	16957		14972		13216		11368	

*denotes studies with available data on death matched to National Death Registries

Supplemental Table A-7b. Comparison of complete-case analysis and imputed analysis of mortality rate ratio between women and men at 1 year and 5 years after stroke

Study	Unadjusted		Adjusted for confounders	
	Complete-case MRR (95% CI)	**Imputed*** MRR (95% CI)	**Complete-case** MRR (95% CI)	**Imputed*** MRR (95% CI)
Melbourne				
1-year	1.42 (1.10-1.84)	1.52 (1.26-1.83)	0.76 (0.50-1.15)	0.89 (0.61-1.28)
5-year	1.34 (1.09-1.64)	1.42 (1.19-1.70)	0.69 (0.47-1.01)	0.85 (0.65-1.11)
Pooled data				
1-year (13 studies)	1.35 (1.24-1.47)	1.37 (1.26-1.48)	0.81 (0.72-0.92)	0.82 (0.73-0.93)
5-year (8 studies)	1.24 (1.12-1.38)	1.28 (1.15-1.42)	0.76 (0.65-0.89)	0.78 (0.67-0.91)

MRR (95% CI), Mortality rate ratio (95% confidence interval)
*using multiple imputation as described in supplementary methods

Supplemental Table A-8. Sensitivity analysis of long-term mortality rate ratio between women and men among studies with data on date of death at 1 year (n=11 studies) and 5 years (n=6 studies) after stroke excluding early deaths (1 month, 3 months and 6 months)

Study	Excluding 1-month deaths					Excluding 3-month deaths					Excluding 6-month deaths				
	N*	Unadjusted		Adjusted		N*	Unadjusted		Adjusted		N*	Unadjusted		Adjusted	
		MRR	(95% CI)	MRR	(95% CI)		MRR	(95% CI)	MRR	(95% CI)		MRR	(95% CI)	MRR	(95% CI)
1-year outcome															
Oxford	1112	**1.62**	**(1.18-2.24)**	0.87	(0.60-1.14)	1054	1.32	(0.89-1.94)	0.69	(0.47-1.02)	1009	1.37	(0.81-2.30)	0.75	(0.45-1.27)
Joinville	891	0.96	(0.64-1.44)	0.79	(0.52-1.22)	855	1.14	(0.69-1.90)	0.95	(0.57-1.60)	827	1.53	(0.75-3.11)	1.33	(0.68-2.59)
Melbourne	789	**1.45**	**(1.01-2.08)**	0.91	(0.60-1.39)	738	1.44	(0.91-2.27)	0.95	(0.56-1.59)	701	1.20	(0.64-2.25)	0.82	(0.44-1.53)
Arcadia	428	1.33	(0.86-1.98)	1.10	(0.73-1.65)	412	1.25	(0.81-1.94)	1.05	(0.68-1.63)	400	1.23	(0.76-1.99)	1.05	(0.66-1.70)
Perth	148	0.59	(0.27-1.28)	**0.43**	**(0.20-0.95)**	137	0.50	(0.19-1.33)	0.45	(0.15-1.34)	132	0.31	(0.08-1.11)	0.25	(0.06-1.05)
Orebro	308	1.52	(0.87-2.64)	1.10	(0.61-1.99)	288	1.59	(0.81-3.15)	1.21	(0.60-2.43)	268	1.42	(0.51-3.95)	1.19	(0.42-3.36)
Dijon	3477	1.17	(0.98-1.40)	**0.78**	**(0.63-0.97)**	3286	1.03	(0.82-1.29)	**0.69**	**(0.54-0.90)**	3151	0.93	(0.70-1.25)	**0.67**	**(0.50-0.89)**
Porto	556	1.56	(0.97-2.50)	0.90	(0.54-1.50)	552	1.48	(0.81-2.71)	0.79	(0.41-1.52)	506	0.89	(0.43-1.82)	**0.41**	**(0.20-0.85)**
Auckland	950	1.34	(0.92-1.96)	0.83	(0.56-1.25)	905	1.54	(0.95-2.51)	1.02	(0.60-1.73)	879	1.73	(0.92-3.23)	1.21	(0.62-2.37)
Pooled	8,659	**1.29**	**(1.11-1.48)**	**0.84**	**(0.74-0.95)**	8,227	**1.19**	**(1.04-1.37)**	0.81	**(0.70-0.95)**	7,873	1.14	(0.92-1.40)	0.82	(0.64-1.04)
		I^2=23.5%	p=0.235	I^2=0.0%	p=0.663		I^2=0.0%	p=0.442	I^2=0.0%	p=0.524		I^2=14.5%	p=0.313	I^2=31.9%	p=0.162
5-year outcome															
Oxford	619	1.11	(0.85-1.45)	**0.68**	**(0.51-0.90)**	583	1.00	(0.75-1.32)	**0.65**	**(0.49-0.87)**	562	0.98	(0.73-1.32)	**0.67**	**(0.50-0.89)**
Melbourne	789	**1.27**	**(1.01-1.60)**	0.86	(0.68-1.10)	738	1.44	(0.91-2.27)	0.95	(0.56-1.59)	701	1.17	(0.90-1.50)	0.83	(0.65-1.06)
Orebro	308	**1.44**	**(1.03-2.02)**	1.02	(0.72-1.45)	288	**1.43**	**(1.01-2.03)**	1.02	(0.72-1.45)	268	1.37	(0.94-1.97)	1.00	(0.70-1.44)
Dijon	2702	1.03	(0.91-1.16)	**0.73**	**(0.63-0.86)**	2568	0.94	(0.70-1.25)	**0.61**	**(0.45-0.83)**	2468	0.97	(0.84-1.11)	**0.71**	**(0.60-0.83)**
Porto	556	1.03	(0.77-1.34)	**0.65**	**(0.48-0.87)**	522	1.48	(0.81-2.71)	0.79	(0.41-1.52)	506	0.83	(0.61-1.12)	**0.54**	**(0.40-0.74)**
Auckland	950	**1.36**	**(1.02-1.83)**	0.86	(0.62-1.19)	905	**1.44**	**(1.04-2.00)**	0.95	(0.67-1.36)	879	**1.46**	**(1.03-2.08)**	1.00	(0.69-1.46)
Pooled	5,924	**1.15**	**(1.02-1.30)**	**0.77**	**(0.69-0.87)**	5,604	1.12	(0.97-1.29)	**0.77**	**(0.66-0.89)**	5,384	1.07	(0.92-1.25)	**0.76**	**(0.64-0.89)**
		I^2=32.5%	p=0.192	I^2=19.5%	p=0.286		I^2=49.6%	p=0.077	I^2=44.8%	p=0.107		I^2=49.9%	p=0.076	I^2=53.3%	p=0.057

Bold denotes statistically significant results; MRR (95% CI), Mortality rate ratio (95% confidence interval)

* the sample size were the same among the unadjusted model and adjusted model

Supplemental Table A-9. Prevalence of admission and discharge medication, in-hospital investigation on the exposure of female sex in 13 included studies

	Oxford		Joinville		Melbourne		Arcadia		Perth		Orebro		Dijon		Martinique		Porto		Auckland		L'Aquila		Matão		Tartu	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Admission medication (%)																										
Antihypertensive	-	-	-	-	**50.0**	**57.8**	-	-	51.5	56.2	-	-	46.8	48.5	-	-	-	-	-	-	-	-	-	-	-	-
Antiplatelets	-	-	-	-	30.8	30.6	24.1	26.0	25.8	32.9	-	-	22.8	21.3	-	-	-	-	-	-	-	-	-	-	-	-
Anticoagulants	-	-	-	-	6.0	5.2	**14.3**	**22.5**	**13.6**	**4.1**§	-	-	7.2	6.8	-	-	-	-	-	-	-	-	-	-	-	-
Thrombolysis*	-	-	9.5	7.2	0.0	0.8	-	-	-	-	-	-	11.4‡	9.9‡	-	-	-	-	0.8	0.6	-	-	-	-	-	-
Discharge medication (%)																										
Antihypertensive	-	-	-	-	37.9	37.7	-	-	43.9	31.5	-	-	-	-	-	-	50.0	47.7	60.6	62.9	-	-	-	-	-	-
Antiplatelets*	-	-	-	-	48.3	49.2	-	-	39.6	47.1	-	-	**67.5**	**63.6**	-	-	71.2	67.6	79.9	81.7	-	-	-	-	-	-
Anticoagulants *	-	-	-	-	17.9	14.3	-	-	22.6	10.2§	-	-	14.1	15.8	-	-	-	-	15.9	13.8	-	-	-	-	-	-
Investigation (%)																										
Neuroimaging	-	-	100.0	100.0	94.3	92.8	87.4	81.9	97.0	93.2	89.8	84.2	98.2	97.7	95.9	94.9	99.3	99.5	93.9	92.3	81.5	82.3	100.0	100.0	100.0	96.4
Electrocardiography-ECG	-	-	99.0	98.9	89.7	87.3	100.0	100.0	92.4	97.2	-	-	98.5	98.5	-	-	93.6	91.5	-	-	100.0	100.0	100.0	100.0	74.4	76.8
Carotid investigation*	-	-	**89.8**	**84.0**	50.3	45.4	29.2	25.3	7.6	1.72§	-	-	**95.5**	**93.8**	-	-	46.8	42.4	5.2	3.1	**60.0**	**51.1**	-	-	**24.0**	**8.5**
Echocardiography*	-	-	-	-	**43.8**	**31.7**	19.8	12.7	34.6	19.0	-	-	79.5	78.9	-	-	44.5	38.3	**1.4**	**0.0**§	**17.0**	**14.4**	-	-	-	-
Holter monitor*	-	-	-	-	2.2	3.4	-	-	-	-	-	-	-	-	-	-	4.1	2.8	-	-	3.0	2.3	-	-	-	-
Surgery intervention (%)																										
Carotid endarterectomy*	**5.9**	**2.7**	-	-	1.4	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Coiling/clipping/other†	9.9	17.0	-	-	9.0	7.9	-	-	-	-	-	-	-	-	-	-	-	-	13.7	18.5	-	-	-	-	-	-

Bold numbers denote p-value <0.05; $\chi 2$ test or Fisher's exact test, as appropriate, was used to examine if there were sex differences in admission medication and discharge medication, in-hospital investigation and surgical interventions.

* among ischaemic stroke only; † haemorrhagic stroke; ‡ sample of patients from 2008-2012; § Fisher's exact test

Supplemental Table A-10. Factors contributing to sex difference in long-term mortality between women and men after stroke based on the best fit sex-specific model within studies among hospitalised patients with ischaemic stroke only

Study	1-year		5-year	
	N*	Actual confounding factors used in the fully adjusted model	N*	Actual confounding factors used in the fully adjusted model
Oxford	891	age^3†, NIHSS (2-term)†, pre-stroke mRS	432	age^3†, NIHSS, pre-stroke mRS
Joinville	789	age^3†, log NIHSS†, **carotid investigation**	-	-
Melbourne	733	age, log NIHSS†, pre-stroke Barthel (2-term)†	733	age^3†, NIHSS (2-term)†, pre-stroke Barthel (2-term)†, AF
Arcadia	356	age, GCS, AF	-	-
Perth	112	age, inverse NIHSS†, pre-stroke mRS	-	-
Orebro	262	age, log NIHSS†, institutional residence	262	age, NIHSS^2†, institutional residence
Dijon	3341	age^3†, LOC, AF, smoking	2608	age^3†, LOC, AF, smoking
Martinique	411	age^3†, Barthel at onset (2-term)†, history of PVD	411	age^3†, Barthel at onset (2-term)†
Porto	493	age^3†, LOC, smoking, pre-stroke mRS	493	age^3†, LOC, smoking, pre-stroke mRS^2†
Auckland	849	age^3†, GCS, pre-stroke dependence‡, AF	849	age^3†, GCS, pre-stroke dependence‡, AF
L'Aquila	3076	age, LOC§, AF, smoking	3375	age, LOC§, AF
Matão	79	age§, NIHSS	-	-
Tartu	296	age, log NIHSS	-	-
Total cases	11688		9163	

AF, Atrial fibrillation, GCS, Glasgow Coma Scale; LOC, loss of consciousness (at onset); mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale

* The sample size were the same among the unadjusted model and fully adjusted model

† Transformations were based on the powers (e.g. 3rd power, two power terms) suggested by fractional polynomials that produced the best-fitting multivariable model.

‡ Self-reported data regarding whether the patient lived independently before stroke

§ Not meeting criteria of being a confounder but remain in the fully adjusted multivariable model

Supplemental Table A-11. Sensitivity analysis comparing the pooled adjusted estimates excluding and including carotid investigations included in the study specific model for Joinville

Study	1-year MRR (95% CI)
Joinville	
Crude	1.22 (0.84-1.77)
Adjusted for carotid investigations only	1.08 (0.73-1.60)
Adjusted for confounders, excluding carotid investigations	0.86 (0.56-1.30)
Adjusted for confounders, including carotid investigations	0.76 (0.48-1.21)
Pooled data (13 studies)	
Crude	**1.33 (1.18-1.50)**
Adjusted for confounders, excluding carotid investigations for Joinville	0.84 (0.74-0.95)
Adjusted for confounders, including carotid investigations for Joinville	0.83 (0.73-0.95)

Bold numbers denote p-value <0.05; MRR (95% CI), Mortality rate ratio (95% confidence interval)

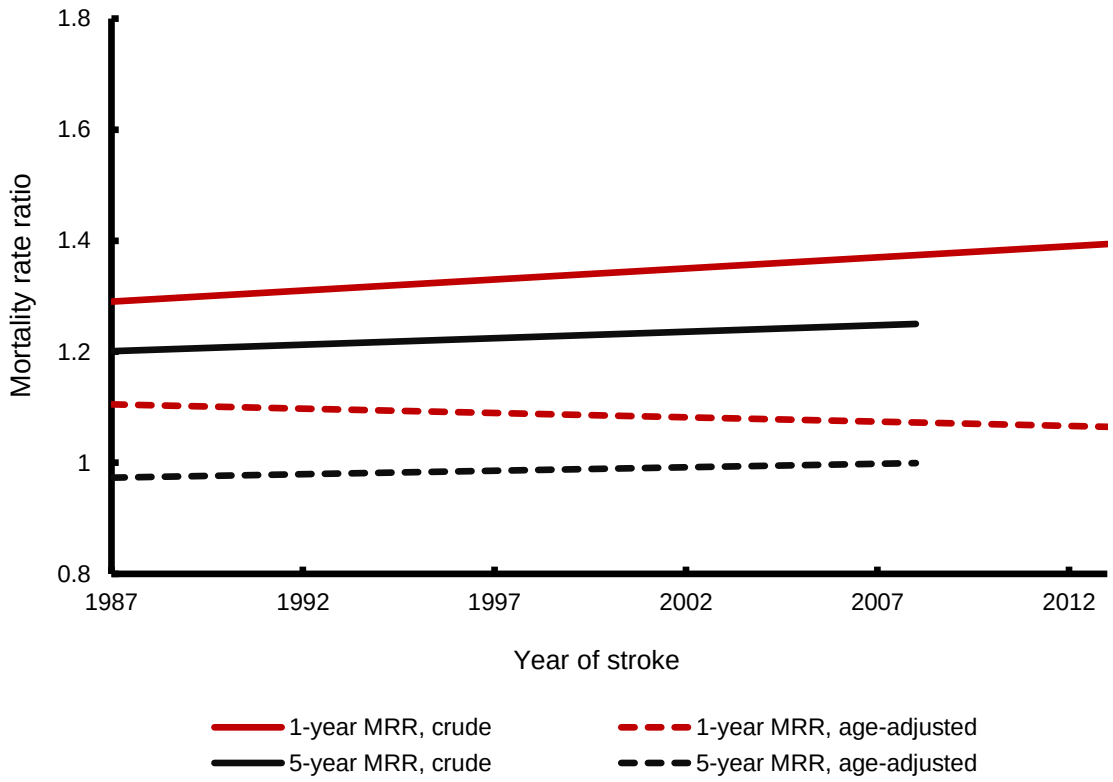


Figure A-1. Mortality rate ratio (MRR) at 1 year (red lines) and 5 years (black lines) for women compared to men by year of stroke occurrence

Appendix B: Sex differences in long-term functional outcome and participation restriction after stroke in the INternational STRoke oUtComes sTudy

Supplemental Table B-1. Baseline characteristic of the 10 included cohort studies, by sex, among survivors followed up to 1 year after stroke

	Oxford		Joinville		Melbourne		Arcadia		Perth		Orebro		Martinique		Porto		Matão		Tartu	
Characteristic	Men n=491	Women n=429	Men n=931	Women n=777	Men n=249	Women n=245	Men n=192	Women n=135	Men n=16	Women n=20	Men n=124	Women n=129	Men n=209	Women n=182	Men n=215	Women n=269	Men n=33	Women n=21	Men n=86	Women n=108
SOCIODEMOGRAPHIC																				
Age, mean (SD)	**70.2 (12.3)**	**73.8 (12.7)**	**61.0 (13.3)**	**62.9 (15.9)**	**70.6 (12.6)**	**73.7 (14.4)**	72.7 (12.4)	73.9 (11.2)	**64.1 (16.5)**	**77.4 (10.7)**	**72.5 (10.9)**	**76.4 (10.5)**	**67.2 (13.7)**	**70.7 (14.3)**	**67.3 (11.3)**	**69.9 (13.6)**	61.8 (10.4)	63.8 (11.2)	**65.5 (10.8)**	**71.4 (11.7)**
Race (%)																				
Caucasian	-	-	-	-	94.4	97.4	-	-	-	-	-	-	-	-	-	-	78.8	90.5	-	-
Non-Caucasian					2.4	1.6											15.2	9.5		
Unknown					3.2	1.2											6.1	0.0		
Marital status (%)																				
Single/widowed	**21.4**	**49.0**	-	-	-	-	-	-	37.5	45.0	**31.5**	**65.1**	-	-	-	-	-	-	-	-
Married	**69.9**	**43.8**							62.5	55.0	**68.6**	**34.9**								
Unknown	**8.7**	**7.2**							0.0	0.0	**0.0**	**0.0**								
Education level (%)																				
≤ Grade 12	69.7	73.7	93.3	93.4	66.3	78.0	-	-	-	-	-	-	-	-	82.3	75.8	75.8	100.0	-	-
> Grade 12	16.8	12.4	6.6	6.4	26.1	20.0									3.7	2.2	15.2	0.0		
Unknown	13.5	14.0	0.1	0.1	7.6	2.0									14.0	21.9	9.1	0.0		
Social class (%)																				
Professional	**18.3**	**7.7**	-	-	36.1	35.9	-	-	25.0	20.0	-	-	30.6	19.8	**24.7**	**13.8**	-	-	-	-
Non-manual	**21.6**	**35.7**			13.7	13.9			12.5	25.0			41.7	59.9	**69.3**	**70.3**				
Manual	**44.5**	**37.3**			47.4	46.5			56.3	35.0			7.7	20.3	**1.4**	**9.7**				
Unknown	**15.6**	**19.4**			2.8	3.7			6.3	20.0			0.0	0.0	**4.7**	**6.3**				
PRE-STROKE HEALTH																				
In an institution (%)																				
Yes	-	-	-	-	4.4	8.6	-	-	**0.0**	**35.0**	**1.6**	**7.8**	-	-	-	-	-	-	-	-
No					95.6	91.0			**100**	**65.0**	**98.4**	**92.3**								
Unknown					0.0	0.4			**0.0**	**0.0**	**0.0**	**0.0**								
Modified Rankin Score (%)																				
0-2	**91.7**	**84.2**	-	-	-	-	99.5	100.0	**93.8**	**50.0**	-	-	-	-	**96.3**	**88.5**	-	-	-	-
3-5	**8.1**	**15.6**					0.5	0.0	**0.0**	**50.0**					**3.7**	**8.9**				
Unknown	**0.2**	**0.2**					0.0	0.0	**6.3**	**0.0**					**0.0**	**2.6**				
Barthel Index score (%)																				
20	-	-	-	-	**84.3**	**74.7**	-	-	**93.8**	**40.0**	91.9	11.7	-	-	-	-	-	-	-	-
<20					**12.5**	**21.2**			**0.0**	**60.0**	8.1	87.6								
Unknown					**3.2**	**4.1**			**6.3**	**0.0**	0.0	0.8								

Supplemental Table B-1. Baseline characteristic of the 10 included cohort studies, by sex, among survivors followed up to 1 year after stroke

	Oxford		Joinville		Melbourne		Arcadia		Perth		Orebro		Martinique		Porto		Matão		Tartu	
Characteristic	Men n=491	Women n=429	Men n=931	Women n=777	Men n=249	Women n=245	Men n=192	Women n=135	Men n=16	Women n=20	Men n=124	Women n=129	Men n=209	Women n=182	Men n=215	Women n=269	Men n=33	Women n=21	Men n=86	Women n=108
Modified Rankin Score, mean (SD)	**0.73 (0.99)**	**1.08 (1.12)**	-	-	-	-	0.27 (0.55)	0.27 (0.55)	**0.3 (0.7)**	**2.3 (1.2)**	-	-	-	-	**0.3 (0.7)**	**0.7 (1.0)**				
Barthel Index, mean (SD)	-	-	-	-	**19.6 (1.5)**	**19.1 (2.7)**	-	-	19.3 (2.8)	16.5 (6.2)	19.6 (1.4)	19.2 (2.9)	-	-	-	-	-	-	-	-
MEDICAL HISTORY																				
Hypertension (%)																				
Yes	59.9	61.8	**62.0**	**69.8**	51.0	59.6	78.2	84.4	37.5	55.0	30.7	43.4	**62.7**	**74.2**	**55.8**	**68.8**	69.7	71.4	67.4	75.0
No	39.9	38.2	**38.0**	**30.2**	49.0	40.4	21.8	15.6	62.5	35.0	67.7	55.0	**36.4**	**23.6**	**44.2**	**31.2**	27.3	28.6	32.6	25.0
Unknown	0.2	0.0	**0.0**	**0.0**	0.0	0.0	0.0	0.0	0.0	10.0	1.6	1.6	**1.0**	**2.2**	**0.0**	**0.0**	3.0	0.0	0.0	0.0
Atrial fibrillation (%)																				
Yes	16.8	16.3	3.3	3.1	15.7	17.1	26.4	32.6	12.5	20.0	15.3	16.3	10.5	11.0	9.8	8.6	3.0	0.0	17.4	28.7
No	83.2	83.7	96.7	96.9	83.1	82.9	73.6	67.4	87.5	75.0	84.7	83.7	88.5	86.8	90.2	91.4	90.9	100.0	82.6	71.3
Unknown	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	5.0	0.0	0.0	1.0	2.2	0.0	0.0	6.1	0.0	0.0	0.0
Ischaemic heart disease (%)																				
Yes	**14.1**	**7.9**	**5.6**	**2.5**	16.9	9.0	15.0	16.3	25.0	5.0	20.2	15.5	5.3	5.0	7.9	8.9	6.1	0.0	29.1	29.6
No	**85.7**	**92.1**	**94.4**	**97.6**	83.1	91.0	85.0	83.7	75.0	95.0	79.8	84.5	93.8	92.9	92.1	91.1	97.9	100.0	70.9	70.4
Unknown	**0.2**	**0.0**	**0.0**	**0.0**	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	2.2	0.0	0.0	6.1	0.0	0.0	0.0
Peripheral vascular disease (%)																				
Yes	6.7	4.4	-	-	**10.0**	**4.5**	8.8	8.2	-	-	35.5	21.7	7.7	11.0	**7.0**	**4.5**	0.0	4.8	-	-
No	92.9	95.1			**90.0**	**85.5**	91.2	91.9			64.5	78.3	91.4	86.8	**86.5**	**80.7**	93.9	95.2		
Unknown	0.4	0.5			**0.0**	**0.0**	0.0	0.0			0.0	0.0	1.0	2.2	**6.5**	**14.9**	6.1	0.0		
Transient ischaemic attack (%)																				
Yes	12.9	12.1	2.4	1.9	10.0	11.0	18.7	14.1	31.3	15.0	**15.3**	**14.0**	3.4	7.1	10.7	8.2	6.1	0.0	29.1	26.9
No	87.1	87.7	97.6	98.1	89.6	89.0	81.4	85.9	62.5	85.0	**84.7**	**86.1**	62.7	57.7	89.3	91.8	97.9	100.0	70.9	70.4
Unknown	0.0	0.2	0.0	0.0	0.4	0.0	0.0	0.0	6.3	0.0	**0.0**	**0.0**	34.0	35.2	0.0	0.0	6.1	0.0	0.0	0.0
Diabetes (%)																				
Yes	14.6	10.3	-	-	18.9	15.9	23.8	33.3	18.8	20.0	17.7	18.6	-	-	-	-	-	-	-	-
No	85.5	89.7			80.7	84.1	76.2	66.7	81.3	80.0	81.5	80.6								
Unknown	0.0	0.0			0.4	0.0	0.0	0.0	0.0	0.0	0.8	0.8								
Dementia (%)																				
Yes	-	-	-	-	**2.0**	**6.5**	-	-	-	-	3.2	7.0	-	-	-	-	0.0	4.8	-	-
No					**75.9**	**72.2**					96.8	93.0					93.9	95.2		
Unknown					**22.1**	**21.2**					0.0	0.0					6.1	0.0		
Smoking (%)																				
Current	**51.4**	**27.5**	**30.5**	**14.5**	**51.0**	**21.2**	**32.6**	**1.5**	**68.8**	**35.0**	**29.8**	**18.6**	**15.8**	**0.0**	**21.4**	**0.7**	**51.5**	**14.3**	-	-
Former	**18.5**	**16.6**	**40.5**	**18.5**	**16.1**	**13.5**	-	-	**18.8**	**5.0**	**66.1**	**81.4**	-	-	**32.1**	**4.5**	-	-		
Never	**29.9**	**55.0**	**29.0**	**66.9**	**32.1**	**62.9**	**67.4**	**98.5**	**0.0**	**55.0**	-	-	**83.3**	**97.8**	**46.5**	**94.8**	**45.5**	**85.7**		
Unknown	**0.2**	**0.9**	**0.0**	**0.0**	**0.8**	**2.5**	**0.0**	**0.0**	**12.5**	**5.0**	**4.0**	**0.0**	**1.0**	**2.2**	**0.0**	**0.0**	**3.0**	**0.0**		
Alcohol use (%)																				

Supplemental Table B-1. Baseline characteristic of the 10 included cohort studies, by sex, among survivors followed up to 1 year after stroke

	Oxford		Joinville		Melbourne		Arcadia		Perth		Orebro		Martinique		Porto		Matão		Tartu	
Characteristic	Men n=491	Women n=429	Men n=931	Women n=777	Men n=249	Women n=245	Men n=192	Women n=135	Men n=16	Women n=20	Men n=124	Women n=129	Men n=209	Women n=182	Men n=215	Women n=269	Men n=33	Women n=21	Men n=86	Women n=108
Non-drinkers	**26.0**	**55.0**	**47.9**	**80.8**	**18.9**	**44.1**	**79.8**	**98.5**	18.8	25.0	-	-	**74.6**	**93.4**	**28.4**	**66.2**	**72.7**	**100.0**	-	-
Not heavy drinkers	**67.2**	**38.7**	**40.9**	**17.9**	**65.9**	**50.0**	-	-	0.0	25.0			-	-	-	-	-	-		
Heavy drinkers	**3.3**	**2.3**	**11.2**	**1.3**	**7.6**	**1.2**	**20.2**	**1.5**	56.3	30.0			**24.4**	**4.4**	**67.4**	**20.5**	**21.2**	**0.0**		
Ex-drinkers	-	-	-	-	**6.0**	**0.4**	-	-	12.5	10.0			-	-	-	-	-	-		
Unknown	**3.5**	**4.0**	**0.0**	**0.0**	**1.6**	**4.1**	**0.0**	**0.0**	12.5	10.0			**1.0**	**2.2**	**4.2**	**13.4**	**6.1**	**0.0**		
Body mass index, mean (SD)	26.6 (4.5)	26.5 (5.6)	26.8 (4.4)	26.8 (5.2)	-	-	-	-	NA	NA	-	-	-	-	26.3 (3.7)	26.7 (5.3)	-	-		
Medication																				
Antihypertensives (%)																				
Yes	-	-	**56.1**	**66.0**	51.0	58.0	-	-	25.0	45.0	-	-	-	-	-	-	-	-	-	-
No			**43.9**	**34.1**	48.6	42.0			75.0	40.0										
Unknown			**0.0**	**0.0**	0.4	0.0			0.0	15.0										
Antiplatelet (%)																				
Yes	-	-	24.7	28.8	33.3	31.8	-	-	25.0	45.0	-	-	-	-	-	-	-	-	-	-
No			75.3	71.2	66.3	68.2			68.8	50.0										
Unknown			0.0	0.0	0.0	0.0			6.3	5.0										
STROKE-RELATED FACTORS																				
Hospital admission (%)																				
Yes	81.3	80.7	100.0	100.0	95.2	94.3	91.2	94.8	93.8	70.0	97.6	92.3	91.9	92.3	97.2	96.3	100.0	100.0	96.5	91.7
No	18.7	19.4	0.0	0.0	4.8	5.7	8.8	5.2	6.3	30.0	2.4	7.8	8.1	7.7	2.8	3.7	0.0	0.0	3.5	8.3
Time to arrive hospital (%), hospitalised																				
≤ 4.5 hours	-	-	41.4	42.2	25.3	21.2	-	-	13.3	21.4	-	-	82.3	78.6	39.2	35.5	-	-	33.7	33.3
> 4.5 – 24 hours			28.7	25.5	12.1	12.2			6.7	14.3			-	-	32.5	38.2			7.2	3.0
> 24 hours			28.8	29.7	8.4	6.9			6.7	21.4			17.7	21.4	19.1	15.8			4.8	4.0
Unknown			1.4	2.6	54.2	59.6			73.3	42.9			0.0	0.0	9.1	10.4			54.2	59.6
Stroke type (%)																				
Ischaemic stroke	**90.0**	**85.3**	**67.8**	**69.1**	**85.9**	**84.9**	74.6	77.8	75.0	80.0	**83.1**	**84.5**	80.4	82.4	81.4	80.7	84.9	100.0	86.1	83.3
Intracerebral haemorrhage	**4.6**	**5.1**	**8.0**	**5.9**	**12.1**	**8.2**	12.4	7.4	6.3	0.0	**14.5**	**7.8**	13.4	8.2	13.0	12.6	15.2	0.0	11.6	8.3
Subarachnoid haemorrhage	**1.0**	**5.4**	**3.9**	**6.4**	**0.0**	**0.4**	0.5	3.0	12.5	5.0	**0.0**	**0.0**	2.9	4.4	1.9	4.1	0.0	0.0	0.0	0.0
Undetermined	**4.4**	**4.2**	**20.4**	**18.5**	**2.0**	**6.5**	12.4	11.9	6.3	15.0	**2.4**	**7.8**	3.4	5.0	3.7	2.6	0.0	0.0	2.3	8.3
Stroke severity																				
NIHSS, mean (SD)	**3.5 (4.4)**	**4.0 (5.2)**	5.6 (6.2)	6.0 (6.6)	4.8 (5.1)	5.6 (5.7)	-	-	5.0 (5.7)	6.6 (7.3)	5.4 (5.3)	5.6 (4.8)	-	-	-	-	**5.6 (5.1)**	**8.7 (5.9)**	5.0 (6.5)	6.2 (6.5)
Glasgow Coma Scale, reversed, mean (SD)	-	-	-	-	-		**3.8 (1.7)**	**4.0 (2.1)**	-	-	-	-	-	-	7.2 (7.5)	8.3 (7.9)	-	-	-	-
Loss of consciousness (%)																				
Yes	-	-	-	-	7.6	11.4	6.7	5.2	-	-	-	-	-	-	0.0	1.1	-	-	-	-

Supplemental Table B-1. Baseline characteristic of the 10 included cohort studies, by sex, among survivors followed up to 1 year after stroke

	Oxford		Joinville		Melbourne		Arcadia		Perth		Orebro		Martinique		Porto		Matão		Tartu	
Characteristic	Men n=491	Women n=429	Men n=931	Women n=777	Men n=249	Women n=245	Men n=192	Women n=135	Men n=16	Women n=20	Men n=124	Women n=129	Men n=209	Women n=182	Men n=215	Women n=269	Men n=33	Women n=21	Men n=86	Women n=108
No					70.3	66.9	84.5	89.6							100.0	98.9				
Unknown					22.1	21.6	8.8	5.2							0.0	0.0				
Body paralysis (%)																				
Yes	-	-	-	-	16.5	22.0	19.2	19.3	-	-	-	-	-	-	70.2	70.2	-	-	-	-
No					61.5	56.7	72.0	75.6							29.8	29.4				
Unknown					22.1	21.2	8.8	5.2							0.0	0.0				
Incontinence (%)																				
Yes	-	-	-	-	9.6	12.7	5.7	7.4	-	-	-	-	-	-	-	-	-	-	-	-
No					87.2	86.5	85.5	87.4												
Unknown					3.2	0.8	8.8	5.2												
Barthel at onset (%)																				
> 60	-	-	-	-	-	-	-	-	-	-	-	-	59.3	52.2	-	-	-	-	-	-
≤ 60													24.4	31.9						
Unknown													16.3	15.9						
POST-STROKE FACTORS																				
Depression at 1 year																				
Yes	-	-	-	-	15.7	16.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
No					69.1	62.0														
Unknown					15.3	21.6														
Recurrence at 1 year																				
Yes	7.7	10.0	-	-	0.8	0.4	7.8	6.7	-	-			6.2	10.4	7.9	6.7	18.2	9.5	-	-
No	92.3	90.0			99.2	99.6	92.2	93.3					93.8	89.6	92.1	93.3	75.8	90.5		
Unknown	0.0	0.0			0.0	0.0	0.0	0.0					0.0	0.0	0.0	0.0	0.0	0.0		

Bold denotes statistically significant results between women and men; NIHSS, National Institutes of Health Stroke Scale.

* among hospitalised patients

Supplemental Table B-2. Baseline characteristic of 7 included cohort studies, by sex, among survivors followed up to 5 years after stroke

Characteristic	Oxford		Joinville		Melbourne		Martinique		Porto		Auckland		Tartu	
	Men n=195	Women n=190	Men n=245	Women n=178	Men n=232	Women n=228	Men n=150	Women n=115	Men n=111	Women n=148	Men n=163	Women n=140	Men n=53	Women n=61
SOCIODEMOGRAPHIC														
Age, mean (SD)	**68.4 (11.0)**	**71.4 (11.7)**	57.8 (14.0)	58.7 (14.9)	68.1 (13.3)	70.4 (15.1)	65.6 (12.7)	66.1 (13.7)	63.3 (11.3)	64.6 (13.6)	**64.0 (12.5)**	**68.6 (12.4)**	**61.1 (11.4)**	**67.9 (12.6)**
Race (%)														
Caucasian	-	-	-	-	**91.0**	**96.1**	-	-	-	-	-	-	-	-
Non-Caucasian					**3.5**	**2.6**								
Unknown					**5.6**	**1.3**								
Ethnicity (%)														
New Zealand/European	-	-	-	-	-	-	-	-	-	-	73.7	78.2	-	-
Non-NZ/European											26.3	21.8		
Marital status (%)														
Single/widowed	**21.0**	**49.0**	-	-	-	-	-	-	-	-	-	-	-	-
Married	**68.7**	**43.7**												
Unknown	**10.3**	**7.4**												
Education level (%)														
≤ Grade 12	75.4	77.9	93.1	91.0	53.9	62.7	-	-	85.6	83.8	35.6	59.3	-	-
> Grade 12	13.3	11.1	6.9	9.0	37.9	35.1			3.6	2.0	54.6	35.7		
Unknown	11.3	11.1	0.0	0.0	8.2	2.2			10.8	14.2	9.8	5.0		
Social class (%)														
Professional	**12.8**	**5.3**	-	-	37.1	34.7	**35.3**	**25.2**	**37.0**	**23.0**	**28.8**	**18.6**	-	-
Non-manual	**17.4**	**30.5**			10.8	11.8	**58.7**	**53.9**	**54.1**	**59.5**	**13.5**	**28.6**		
Manual	**51.3**	**45.3**			42.7	38.2	**6.0**	**20.9**	**1.8**	**12.2**	**50.3**	**14.3**		
Unknown	**18.5**	**19.0**			9.5	15.4	**0.0**	**0.0**	**7.2**	**5.4**	**7.4**	**28.6**		
PRE-STROKE HEALTH														
In an institution (%)														
Yes	-	-	-	-	**2.2**	**7.5**	-	-	-	-	-	-	-	-
No					**96.6**	**91.2**								
Unknown					**1.3**	**1.3**								
Modified Rankin Score (%)														
0-2	**95.9**	**89.0**	-	-	-	-	-	-	97.3	93.2	-	-	50.0	60.0
3-5	**4.1**	**11.1**							2.7	6.1			0.0	40.0
Unknown	**0.0**	**0.0**							0.0	0.7			0.0	0.0
Barthel Index score (%)														
20	-	-	-	-	**72.8**	**64.9**	-	-	-	-	-	-	-	-
<20					**6.9**	**14.0**								
Unknown					**20.3**	**21.1**								
Modified Rankin Score, mean (SD)	**0.6 (0.8)**	**1.0 (1.0)**			-	-	-	-	**0.2 (0.6)**	**0.6 (0.9)**	-	-	0.6 (0.9)	0.8 (0.4)
Barthel Index, mean (SD)	-	-	-	-	**19.8 (1.0)**	**19.4 (2.0)**	-	-	-	-	-	-	-	-
Pre-stroke dependence (%)														
Yes	-	-	-	-	-	-	-	-	-	-	**2.4**	**9.3**	-	-
No											**96.9**	**90.7**		
Unknown											**0.6**	**0.0**		
MEDICAL HISTORY														
Hypertension (%)														
Yes	55.9	62.6	58.0	65.2	51.7	57.9	59.3	72.2	56.8	73.0	**56.4**	**57.1**	**80.0**	**35.0**
No	44.1	37.4	42.0	34.8	47.4	42.1	39.3	27.0	43.2	27.0	**42.9**	**42.1**	**20.0**	**65.0**
Unknown	0.0	0.0	0.0	0.0	0.9	0.0	1.3	0.9	0.0	0.0	**0.6**	**0.7**	**0.0**	**0.0**
Atrial fibrillation (%)														
Yes	13.9	12.6	0.0	0.0	12.9	15.4	10.7	9.6	7.2	5.4	10.4	20.0	40.0	10.0
No	86.2	87.4	100.0	100.0	86.2	84.7	88.0	89.6	92.8	94.6	89.6	80.0	60.0	90.0
Unknown	0.0	0.0	0.0	0.0	0.9	0.0	1.3	0.9	0.0	0.0	0.0	0.0	0.0	0.0
Ischaemic heart disease (%)														
Yes	12.8	6.3	0.0	0.0	13.4	8.3	4.0	5.2	5.4	6.1	19.6	12.9	30.0	10.0
No	86.7	93.7	100.0	100.0	85.8	91.7	94.7	93.9	94.6	93.9	80.4	87.1	70.0	90.0
Unknown	0.5	0.0	0.0	0.0	0.9	0.0	1.3	0.9	0.0	0.0	0.0	0.0	0.0	0.0

Supplemental Table B-2. Baseline characteristic of 7 included cohort studies, by sex, among survivors followed up to 5 years after stroke

Characteristic	Oxford		Joinville		Melbourne		Martinique		Porto		Auckland		Tartu	
	Men n=195	Women n=190	Men n=245	Women n=178	Men n=232	Women n=228	Men n=150	Women n=115	Men n=111	Women n=148	Men n=163	Women n=140	Men n=53	Women n=61
Peripheral vascular disease (%)														
Yes	7.2	4.7	-	-	6.9	3.5	6.7	9.6	4.5	4.7	-	-	-	-
No	92.8	95.3			92.2	96.1	92.0	89.6	89.2	83.8				
Unknown	0.0	0.0			0.9	0.4	1.3	0.9	6.3	11.5				
Transient ischaemic attack (%)														
Yes	13.3	16.3	0.0	0.0	8.2	9.2	4.0	6.1	9.9	8.8	-	-	0.0	15.0
No	86.7	83.7	100.0	100.0	91.4	90.4	64.0	67.0	90.1	91.2			100.0	85.0
Unknown	0.0	0.0	0.0	0.0	0.4	0.4	32.0	27.0	0.0	0.0			0.0	00.0
Diabetes (%)														
Yes	11.8	6.8	-	-	20.3	15.8	-	-	-	-	-	-	-	-
No	88.2	93.2			78.9	84.2								
Unknown	0.0	0.0			0.9	0.0								
Dementia (%)														
Yes	-	-	-	-	**0.0**	**4.0**	-	-	-	-	0.6	0.0	-	-
No					**78.9**	**76.3**					99.4	100.0		
Unknown					**21.1**	**19.7**					0.0	0.0		
Smoking (%)														
Current	**50.3**	**25.8**	**31.0**	**15.2**	**31.5**	**59.7**	**18.0**	**0.0**	**23.4**	**1.4**	**58.9**	**53.6**	-	-
Former	**22.6**	**20.0**	**36.7**	**15.7**	**47.4**	**21.1**	-	-	-	-	**11.0**	**7.9**		
Never	**27.1**	**53.7**	**32.2**	**69.1**	**16.4**	**13.6**	**80.7**	**99.1**	**23.4**	**93.9**	**19.5**	**53.6**		
Unknown	**0.0**	**0.5**	**0.0**	**0.0**	**4.7**	**5.7**	**1.3**	**0.9**	**27.0**	**4.7**	**0.6**	**0.0**		
Alcohol use (%)														
Non-drinkers	**24.6**	**51.6**	**38.0**	**73.0**	**17.2**	**46.9**	**74.0**	**94.8**	**23.4**	**66.9**	**16.6**	**41.4**	-	-
Not heavy drinkers	**69.2**	**40.5**	**47.8**	**25.3**	**61.2**	**43.0**	-	-	-	-	**71.8**	**42.9**		
Heavy drinkers	**4.1**	**4.7**	**14.3**	**1.7**	**9.1**	**1.8**	**24.7**	**4.4**	**73.9**	**24.3**	**10.4**	**15.0**		
Ex-drinkers	-	-	-	-	**6.5**	**0.1**	-	-	-	-	-	-		
Unknown	**2.1**	**3.2**	**0.0**	**0.0**	**6.0**	**7.9**	**1.3**	**0.9**	**2.7**	**9.8**	**1.2**	**0.7**		
Body mass index, mean (SD)	26.4 (4.5)	26.9 (5.5)	26.8 (4.0)	26.7 (5.0)	-	-	-	-	26.9 (3.6)	26.9 (5.6)	-	-	-	-
Medication														
Antihypertensives (%)														
Yes	-	-	**51.4**	**61.8**	48.3	53.5	-	-	-	-	42.9	42.1	-	-
No			**48.6**	**38.2**	51.3	45.6					4.9	7.1		
Unknown			**0.0**	**0.0**	0.4	0.9					52.2	50.7		
Antiplatelet (%)														
Yes	-	-	23.3	24.2	29.3	29.4	-	-	-	-	32.5	28.6	-	-
No			76.7	75.8	70.3	70.2					66.9	70.7		
Unknown			0.0	0.0	0.4	0.4					0.6	0.7		
STROKE-RELATED FACTORS														
Hospital admission (%)														
Yes	64.1	63.7	100.0	100.0	92.2	94.3	90.7	93.9	97.3	96.0	96.9	95.0	80.0	55.0
No	35.9	36.3	0.0	0.0	7.8	5.7	9.3	6.1	2.7	4.1	3.1	5.0	20.0	45.0
Time to arrive hospital* (%)														
≤ 4.5 hours	-	-	43.7	46.1	24.3	24.7	83.8	77.8	36.1	37.3	79.8	82.0	25.0	45.5
> 4.5 – 24 hours			26.5	27.5	14.5	8.4			35.2	36.6	-	-	0.0	9.1
> 24 hours			28.6	23.0	7.9	10.2	16.2	22.2	21.3	16.9	13.9	14.3	12.5	0.0
Unknown			1.2	3.4	53.3	56.7	0.0	0.0	7.4	9.2	6.3	7.8	62.5	45.5
Stroke type (%)														
Ischaemic stroke	**92.8**	**84.2**	**72.7**	**68.5**	82.8	85.1	**78.7**	**87.0**	78.4	79.1	82.2	75.7	70.0	45.0
Intracerebral haemorrhage	**3.6**	**4.7**	**7.4**	**9.0**	14.7	10.5	**16.0**	**3.5**	15.3	13.5	8.6	12.1	10.0	15.0
Subarachnoid haemorrhage	**1.5**	**7.4**	**3.3**	**9.6**	0.0	0.0	**3.3**	**4.4**	1.8	4.7	5.5	7.1	-	-
Undetermined	**2.1**	**3.7**	**16.7**	**12.9**	2.6	4.4	**2.0**	**5.2**	4.5	2.7	3.7	5.0	20.0	10.0
Stroke severity														
NIHSS, mean (SD)	3.1 (3.8)	3.5 (5.1)	5.7 (6.3)	6.0 (6.7)	4.3 (4.5)	5.3 (5.6)	-	-	-	-	-	-	5.8 (8.9)	8.3 (7.7)
UNSS, reversed, mean (SD)	-	-	-	-	-	-	-	-	7.3 (7.9)	6.5 (7.0)	-	-	-	-

Supplemental Table B-2. Baseline characteristic of 7 included cohort studies, by sex, among survivors followed up to 5 years after stroke

Characteristic	Oxford		Joinville		Melbourne		Martinique		Porto		Auckland		Tartu	
	Men n=195	Women n=190	Men n=245	Women n=178	Men n=232	Women n=228	Men n=150	Women n=115	Men n=111	Women n=148	Men n=163	Women n=140	Men n=53	Women n n=61
GCS, reversed, mean (SD)	-	-	-	-	-	-	-	-	-	-	1.7 (1.0)	1.8 (2.1)	-	-
Loss of consciousness (%)														
Yes	-	-	-	-	7.8	8.3	-	-	0.0	1.4	25.8	25.7	-	-
No					71.1	71.5			100.0	98.7	73.6	73.6		
Unknown					21.1	20.2	19.1	15.9	0.0	0.0	0.6	0.7		
Body paralysis (%)														
Yes	-	-	-	-	64.2	60.5	14.3	18.8	68.5	69.6	82.8	79.3	-	-
No					14.7	19.7	66.7	65.2	31.5	30.4	17.2	20.7		
Unknown					21.1	19.7	19.1	15.9	0.0	0.0	0.0	0.0		
Incontinence (%)														
Yes	-	-	-	-	5.6	9.7	-	-	-	-	-	-	-	-
No					91.0	90.4								
Unknown					3.5	0.0								
Barthel at onset (%)														
> 60	-	-	-	-	-	-	3.2	11.6	-	-	-	-	-	-
≤ 60							95.2	84.1						
Unknown							1.6	4.4						
POST-STROKE FACTORS														
Depression at 5 years														
Yes	-	-	-	-	11.6	14.0	11.6	14.0	-	-	31.9	31.4	-	-
No					75.4	73.7	75.4	73.7			49.7	47.9		
Unknown					12.9	12.3	12.9	12.3			18.4	207		
Recurrence at 5 years														
Yes	15.4	23.7	-	-	-	-	9.1	9.2	-	-	-	-	-	-
No	84.6	76.3					91.0	90.8						
Unknown	0.0	0.0					0.0	0.0						

Bold denotes statistically significant results between women and men. NIHSS, National Institutes of Health Stroke Scale. UNSS, Unified Neurology Stroke Scale, Glasgow Coma Scale
* among hospitalised patients.

Supplemental Table B-3. List of covariates not meeting the criteria for factors confounding the difference in 1-year functional outcome between women and men

Study	Covariates not meeting the criteria of for confounding factors in univariable model	Confounding factors in univariable model but that were not significant in the final multivariable model*
Oxford	SEP, education, hypertension, AF, IHD, PVD, TIA, diabetes, BMI, smoking, hospital admission, stroke type, recurrence	Marital status, alcohol
Joinville	Race, hypertension, , AF, IHD, PVD, TIA, BMI, smoking, hospital admission, stroke type, pre-stroke medication (antihypertensives, antiplatelet, anticoagulant), delay to hospital	Alcohol
Melbourne	Race, SEP, education, hypertension, IHD, PVD, TIA, diabetes, smoking, alcohol, pre-stroke Barthel*, stroke type, hospital admission, institutional residence, pre-stroke medication (antiplatelet, anticoagulant, antihypertensives), onset LOC, onset incontinence, recurrence (1-year), depression (5-year)	Dementia, onset hemiplegia
Arcadia	hypertension, IHD, PVD, TIA, diabetes, BMI, smoking, alcohol, stroke type, hospital admission, recurrence, onset hemiplegia, onset incontinence, onset LOC	-
Perth	SEP, hypertension, AF, IHD, TIA, diabetes, smoking, alcohol, delay to hospital, pre-stroke medication (antihypertensives, antiplatelet), institutional residence, pre-stroke Barthel, stroke type, hospital admission, severity (NIHSS)*	-
Orebro	Marital status, hypertension, AF, IHD, PVD, TIA, diabetes, dementia, smoking, pre-stroke Barthel, stroke type, hospital admission	-
Martinique	Hypertension, AF, IHD, PVD, TIA, BMI, smoking, alcohol, stroke type, hospital admission, delay to hospital	-
Porto	SEP, education, hypertension, AF, IHD, PVD, TIA, BMI, alcohol, stroke type, stroke severity (UNSS), LOC*, hospital admission, delay to hospital, onset hemiplegia, recurrence	-
Matão	Race, marital status, education, age*, hypertension, AF, IHD, PVD, TIA, smoking, alcohol, stroke type, hospital admission, recurrence	-
Tartu	Hypertension, AF, IHD, TIA, hospital admission, stroke type, delay to hospital, pre-stroke medication (antihypertensives, antiplatelet)	-

* not a confounder but remaining in the final model

AF, Atrial fibrillation; Barthel, Barthel Index; BMI, body mass index; GCS, Glasgow Coma Scale; IHD, ischaemic heart disease; LOC, loss of consciousness (at onset); mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease, TIA, transient ischaemic attack; UNSS, Unified Neurological Stroke Scale; SEP, socioeconomic position

Supplemental Table B-4a. Relative risk of poor functional outcome for women compared to men at 1 year and 5 years after stroke in unadjusted models and models with adjustment for age, severity, and pre-stroke dependency

Study	N*	Unadjusted		Adjusted for age			Adjusted for severity			Adjusted for pre-stroke dependency		
		RR	(95% CI)	RR	(95% CI)	Δ%†	RR	(95% CI)	Δ%†	RR	(95% CI)	Δ%†
1-year outcome												
Oxford	895	**1.45**	**(1.20, 1.75)**	**1.26**	**(1.05, 1.51)**	38%	**1.34**	**(1.12, 1.59)**	21%	**1.21**	**(1.03, 1.44)**	49%
Joinville	1708	**1.42**	**(1.07, 1.90)**	**1.24**	**(1.02, 1.50)**	40%	**1.36**	**(1.13, 1.64)**	13%	-		
Melbourne	415	**1.45**	**(1.18, 1.79)**	**1.30**	**(1.06, 1.58)**	29%	**1.37**	**(1.13, 1.68)**	10%	**1.40**	**(1.13, 1.72)**	4%
Arcadia	327	1.29	(0.93, 1.78)	1.26	(0.91, 1.75)	10%	1.23	(0.89, 1.70)	44%	-		
Perth	36	**6.80**	**(1.80, 25.66)**	**5.18**	**(1.25, 21.6)**	14%	**6.39**	**(1.74, 23.56)**	3%	**5.03**	**(1.25, 20.20)**	16%
Orebro	253	0.94	(0.68, 1.30)	0.80	(0.59, 1.10)	-260%	0.96	(0.71, 1.29)	34%	0.85	(0.62, 1.18)	-162%
Martinique	328	**1.23**	**(0.91, 1.64)**	1.09	(0.82, 1.46)	58%	1.06	(0.82, 1.37)	72%	-		
Porto	477	**1.27**	**(1.02, 1.59)**	1.18	(0.95,1.46)	31%	**1.27**	**(1.02, 1.58)**	0%	1.10	(0.88, 1.36)	60%
Matão	54	1.05	(0.51, 2.14)	**1.06**	**(0.52,2.17)**	-19%	0.84	(0.40, 1.76)	457%	-		
Tartu	164	1.21	(0.81, 1.83)	**0.93**	**(0.63, 0.37)**	138%	1.16	(0.78, 1.73)	22%	1.03	(0.70, 1.52)	84%
Pooled (10 studies)	4657	**1.32**	**(1.18, 1.48)**	**1.17**	**(1.06, 1.30)**	43%	**1.25**	**(1.11, 1.41)**	20%	1.16	(0.98, 1.38)	45%
5-year outcome												
Oxford	378	**1.61**	**(1.25, 2.08)**	**1.39**	**(1.09, 1.78)**	31%	**1.54**	**(1.20, 1.98)**	9%	**1.40**	**(1.10, 1.79)**	29%
Joinville	423	1.20	(0.78, 1.83)	1.09	(0.73, 1.62)	9%	1.15	(0.77, 1.72)	4%	-		
Melbourne	368	1.22	(0.99, 1.51)	1.14	(0.96, 1.36)	34%	1.16	(0.94, 1.43)	25%	1.13	(0.91, 1.40)	39%
Martinique	224	1.17	(0.77, 1.78)	1.14	(0.76, 1.71)	17%	1.02	(0.70, 1.50)	87%	-		
Porto	258	1.14	(0.84, 1.55)	1.05	(0.79, 1.41)	63%	1.14	(0.84, 1.55)	0%	1.05	(0.77, 1.43)	63%
Auckland	302	1.25	(0.86, 1.80)	1.04	(0.72,1.51)	82%	1.27	(0.88, 1.83)	-7%	1.13	(0.78, 1.63)	45%
Tartu	131	**1.79**	**(1.06, 3.02)**	1.44	(0.84, 2.45)	37%	**1.74**	**(1.03, 2.94)**	5%	**1.76**	**(1.04, 2.97)**	3%
Pooled (7 studies)	2,084	**1.31**	**(1.16, 1.47)**	**1.16**	**(1.04, 1.30)**	45%	**1.25**	**(1.11, 1.41)**	17%	**1.22**	**(1.06, 1.41)**	28%

Bold denotes statistically significant results; CI indicates confidence interval; RR, relative risk

* the sample size was the same among the unadjusted model, age-adjusted model, and fully adjusted model

† % change of coefficient of sex difference in relative risk, calculated by the formula (unadjusted β – adjusted β)/unadjusted β *100

Supplemental Table B-4b. Interaction between sex and pre-stroke dependency in functional outcomes after stroke at 1 and 5 years after stroke

Study	Unadjusted					Adjusted for confounding factors				
	Among those dependent before stroke†		Among independent before stroke		$P_{interaction}$	Among those dependent before stroke†		Among independent before stroke		$P_{interaction}$
	RR	**(95% CI)**	**RR**	**(95% CI)**		**RR**	**(95% CI)**	**RR**	**(95% CI)**	
1-year outcome										
Oxford	0.89	0.78, 1.01	**1.48**	**1.17, 1.87**	0.032	0.90	0.78, 1.03	1.20	0.97, 1.49	0.102
Melbourne	0.89	0.70, 1.11	**1.56**	**1.19, 2.03**	0.001	0.92	0.75, 1.13	1.35	0.06, 1.70	0.155
5-year outcome										
Oxford	0.90	0.77, 1.04	**1.61**	**1.21, 2.15**	0.030	0.87	0.71, 1.06	**1.37**	**1.01, 1.72**	0.015
Melbourne	0.95	0.70, 1.29	1.29	0.98, 1.71	0.063	1.16	0.90, 1.49	0.87	0.63, 1.21	0.089

Bold denotes statistically significant results between women and men; CI indicates confidence interval; RR, relative risk of poorer functional outcomes of stroke (modified Rankin Scale>2 for Oxford or Barthel Index for Melbourne <20)

*denotes RR adjusted for confounding factors

†dependence before stroke was defined as modified Rankin Scale>2 for Oxford or Barthel Index for Melbourne <20

Supplemental Table B-5a. Analyses of heterogeneity in functional outcome at 1 year among 10 population-based studies

		No of studies	No of poorer outcome (n/N)		Unadjusted				Adjusted*			
			Men	Women	I^2 (%)	P^H	RR(95% CI)	$P^{sub-group}$	I^2 (%)	P^H	RR(95% CI)	$P^{sub-group}$
Study-level characteristics												
Geographic region	Australasia	2	100/265	156/265	80.2	0.024	2.72 (0.62-12.0)	0.733	75.6	0.043	2.14 (0.56-8.16)	0.432
	Europe	5	343/1099	439/1070	24.1	0.261	1.27 (1.10-1.45)		2.2	0.394	1.04 (0.93-1.16)	
	South America	2	159/964	183/798	0.0	0.414	1.40 (1.15-1.69)		0.0	0.415	1.13 (0.94-1.35)	
	Caribbean	1	78/209	82/182	NA	1.000	1.23 (0.91-1.64)		NA	1.000	0.99 (0.76-1.27)	
Income group	HIC	7	443/1364	595/1335	50.4	0.060	1.32 (1.12-1.54)	0.970	50.7	0.058	1.08 (0.94-1.26)	0.867
	LMIC†	3	237/1173	265/980	0.0	0.550	1.34 (1.14-1.58)		0.0	0.512	1.08 (0.93-1.25)	
Loss to follow-up	≤20%	7	549/2186	661/1942	8.1	0.367	1.30 (1.18-1.44)	0.481	0.0	0.559	1.06 (0.97-1.16)	0.295
	>20%	3	131/351	199/373	66.3	0.052	1.58 (0.99-2.51)		70.8	0.033	1.26 (0.78-2.04)	
Functional outcome measurement	Barthel Index	2	110/282	147/266	0.0	0.389	1.42 (1.16-1.73)	0.641	8.2	0.297	1.21 (0.96-1.52)	0.272
	mRS	8	570/2255	713/2049	42.5	0.095	1.30 (1.14-1.49)		33.1	0.164	1.05 (0.94-1.18)	
Age difference‡	≤4.5 years	7	513/1954	625/1758	4.9	0.390	1.30 (1.17-1.44)	0.431	20.0	0.277	1.09 (0.97-1.21)	0.975
	>4.5 years	3	167/583	235/557	66.3	0.052	1.57 (1.00-2.47)		66.9	0.049	1.16 (0.75-1.80)	
Severity instrument	NIHSS	7	493/2027	607/1756	51.1	0.056	1.35 (1.14-1.59)	0.766	46.6	0.082	1.12 (0.97-1.29)	0.590
	Barthel at onset	1	78/209	82/182	NA	1.000	1.23 (0.91-1.64)		NA	1.000	0.99 (0.76-1.27)	
	Others§	2	109/301	171/377	0.0	0.840	1.26 (1.04-1.53)		0.0	0.509	1.00 (0.82-1.21)	
Pre-stroke function	Unavailable	4	290/1076	312/1115	0.0	0.741	1.33 (1.15-1.54)	0.955	0.0	0.625	1.10 (0.96-1.26)	0.908
	Available	6	390/1171	548/1200	58.4	0.034	1.32 (1.10-1.59)		57.6	0.038	1.07 (0.90-1.26)	

P^H, P-value of heterogeneity; NIHSS, National Institutes of Health Stroke Scale; RR (95% CI), relative risk (95% confidence interval) between women and men; HIC, High-income country; LMIC, Low- and middle-income country

* RR adjusted for actual confounders

† low- and middle-income country (LMIC) group included studies conducted in Joinville, Martinique and Mãtao

‡ indicates difference in median age at onset between women and men

§ other instruments including Glasgow coma scale and loss of consciousness

Supplemental Table B-5b. Testing the interactions between sex and three covariates: time period, age and stroke type using a single pooled IPD dataset in functional outcomes after stroke at 1 year and 5 years after stroke

		Unadjusted			Adjusted for age		
	Covariates	**RR***	**(95% CI)**	**$P_{interaction}$**	**RR**	**(95% CI)**	**$P_{interaction}$**
1-year outcome							
	Stroke type						
	IS	1.38	(1.24-1.54)	Ref	1.19	(1.06-1.35)	Ref
	ICH	1.47	(0.93-2.34)	0.726	1.17	(0.83-1.65)	0.777
	SAH	NA		-	NA		-
	Undetermined	1.03	(0.71-1.50)	0.079	1.04	(0.74-1.45)	0.136
	Age group						
	≤65 years	1.11	(0.90-1.36)	Ref	-		
	>65-75 years	1.22	(1.07-1.39)	0.704	-		
	>75 years	1.10	(0.90-1.35)	0.722	-		
	Year of stroke occurrence						
	1993-2014 (continuous)	1.34	(1.16-1.54)	0.641	1.22	(1.03- 1.44)	0.933
5-year outcome							
	Stroke type						
	IS	1.35	(1.17-1.57)	Ref	1.19	(1.05-1.34)	Ref
	ICH	1.41	(0.75-2.64)	0.999	1.17	(0.60-2.26)	0.884
	SAH	NA		-	NA		-
	Undetermined	1.07	(0.65-1.77)	0.340	0.87	(0.50-1.52)	0.325
	Age group						
	≤65 years	1.29	(0.99-1.67)	Ref	-		
	>65-75 years	1.19	(0.98-1.45)	0.626	-		
	>75 years	1.08	(0.92-1.25)	0.246	-		
	Year of stroke occurrence						
	1996-2011 (continuous)	1.31	(1.19, 1.49)	0.853	1.16	(1.09-1.22)	0.526

NA, not applicable; IS, Ischaemic stroke; ICH, Intracerebral haemorrhage; SAH, Subarachnoid haemorrhage; Ref, Reference group

* RR (95% CI), relative risk (95% confidence interval) of poor functional outcome (mRS>2 or Barthel Index <20)

Supplemental Table B-6. Sensitivity analysis of relative risk of functional outcome between women and men at 1 year and 5 years after stroke. Poor outcome was defined as Barthel Index <20 for Melbourne (or <100 for Matão) or mRS>2 (remaining studies)

Study	Unadjusted		Adjusted for confounders	
	Poor outcome, Barthel <20 (or <100)	Poor outcome, Barthel <19 (or <95)	Poor outcome, Barthel <20 (or <100)	Poor outcome, Barthel <19 (or <95)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Melbourne				
1-year	**1.45 (1.18, 1.79)**	**1.64 (1.27, 2.13)**	**1.25 (1.04, 1.50)**	**1.38 (1.11, 1.73)**
5-year	1.22 (0.99, 1.51)	1.22 (0.96, 1.56)	1.02 (0.84, 1.45)	1.04 (0.93, 1.17)
Matão				
1-year	1.05 (0.51, 2.14)	1.14 (0.55, 2.38)	0.84 (0.40, 1.75)	0.92 (0.43, 1.97)
Pooled data				
1-year, 10 studies	**1.32 (1.18, 1.48)**	**1.34 (1.18, 1.51)**	1.08 (0.97, 1.20)	1.09 (0.97, 1.22)
1-year, 9 studies (excluding Perth*)	**1.33 (1.22, 1.45)**	**1.34 (1.21, 1.47)**	1.08 (1.00, 1.18)	1.08 (0.98, 1.20)
5-year, 7 studies	**1.31 (1.16, 1.47)**	**1.31 (1.16, 1.49)**	1.05 (0.94, 1.18)	1.04 (0.93, 1.17)
5-year, 6 studies (excluding Auckland*)	**1.31 (1.15, 1.50)**	**1.32 (1.15, 1.52)**	1.06 (0.94, 1.19)	1.05 (0.93, 1.19)

Bold denotes statistically significant results between women and men.
RR (95% CI), Relative risk (95% confidence interval)
*studies with greatest missing data

Supplemental Table B-7. Missing data on functional outcome and confounders among the 11 included studies

	1-year				5-year			
Study	**Data available (n)**	**Missing outcome data (%)**	**Assess in full model (n)**	**Missing confounder data (%)**	**Data available (n)**	**Missing outcome data (%)**	**Assess in full model (n)**	**Missing confounder data (%)**
Oxford*	910	7.9%	895	1.6%	385	4.5%	378	1.8%
Joinville	1708	8.6%†	1708	0.0%	423	29.3%†	423	0.0%
Melbourne*	493	38.8%	415	16.0%	460	16.9%	368	20.0%
Arcadia	328	4.1%‡	327	1.8%	-			
Perth*	36	70.0%	36	0.0%	-			
Orebro*	253	0.0%	253	0.0%	-			
Martinique	391	0.0%	328	16.1%	265	0.0%	224	15.4%
Porto	484	0.0%	477	1.4%	259	7.8%	255	1.5%
Auckland	-				303	65.6%§	302	0.3%
Matão*	54	3.6%	54	0.0%	-			
Tartu*	194	20.8%	164	15.5%	131	18.6%	131	0.0%
Total	4,852		4,657		2,226		2,084	

*denotes studies with available data on death matched to National Death Registries

† n=161 cases with missing data on outcome at 1 year (89 cases were lost to follow up and 72 had new stroke events); n=175 cases with missing data on outcome at 5 years (108 were lost to follow up and 67 had new stroke events)

‡ n=14 cases with missing data on outcome (7 cases were lost to follow up (not known died/alive); 7 cases were alive but had no functional outcome assessment)

§ n=578 with missing data on outcome (13.2% of cases were lost to follow-up (not known died/alive); 86.8% were due to other reasons (e.g. refused/not interest, too busy, or changed residence)

Supplemental Table B-8a. Differences in patient characteristics between those with and without functional outcome assessment at 1 year after stroke

	Oxford		**Joinville**		**Melbourne**		**Arcadia**		**Perth**		**Matão**		**Tartu**	
Characteristic	Assessed n=910	Unassessed n=78	Assessed n=1708	Unassessed n=161	Assessed n=494	Unassessed n=312	Assessed n=328	Unassessed n=14	Assessed n=36	Unassessed n=84	Assessed n=54	Unassessed n=2	Assessed n=194	Unassessed n=51
SOCIODEMOGRAPHIC														
Female (%)	47.1	47.4	45.5	43.1	49.6	54.7	41.2	57.1	55.6	53.6	38.9	50.0	55.7	51.0
Age, mean (SD)	71.9 (28.1)	69.8 (16.5)	**61.8 (14.6)**	**66.5 (13.2)**	72.1 (13.6)	69.8 (16.4)	73.2 (11.9)	76.3 (6.6)	71.5 (15.0)	74.2 (12.4)	62.6 (10.7)	64.0 (18.4)	68.7 (11.7)	69.5 (13.0)
Marital status (%)														
Single/widowed	**34.4**	**32.1**	-	-	-	-	-	-	52.8	54.8	-	-	-	-
Married	**5.6**	**41.0**							47.2	41.7				
Unknown	**8.0**	**26.9**							0.0	0.0				
Education level (%)														
≤ Grade 12	71.5	47.4	93.4	94.4	72.1	27.9	-	-	-	-	85.2	100.0	-	-
> Grade 12	14.7	9.0	6.5	2.8	13.1	70.4					9.3	0.0		
Unknown	13.7	43.6	0.1	2.8	4.9	1.7					5.6	0.0		
Social class (%)														
Professional	**13.3**	**5.1**	-	-	36.0	31.3	-	-	22.2	10.7	-	-	-	-
Non-manual	**28.2**	**21.8**			13.8	9.1			19.4	7.1				
Manual	**41.1**	**32.1**			47.0	28.5			44.4	25.0				
Unknown	**17.4**	**41.0**			3.2	31.1			13.9	57.1				
PRE-STROKE HEALTH														
In an institution (%)														
Yes	-	-	-	-	6.5	2.9	-	-	**19.4**	**3.6**	-	-	-	-
No					93.3	88.6			**80.6**	**94.1**				
Unknown					0.2	2.9			**0.0**	**2.4**				
Modified Rankin Score (%)														
0-2	**88.1**	**69.2**	-	-	-	-	99.7	92.9	69.4	72.6	-	-	84.0	56.9
3-5	**11.7**	**14.1**					0.3	7.1	27.8	17.9			3.1	2.0
Unknown	**0.2**	**16.7**					0.0	0.0	2.8	9.5			12.9	41.2
Barthel Index score (%)														
20	-	-	-	-	**79.6**	**25.9**	-	-	63.9	71.4	-	-	-	-
<20					**16.8**	**6.3**			33.3	17.9				
Unknown					**3.6**	**67.8**			2.8	10.7				
MEDICAL HISTORY														
Hypertension (%)														
Yes	60.8	53.9	65.5	72.2	55.3	52.7	80.8	85.7	47.2	63.1	70.4	0.0	**71.7**	**43.1**
No	39.1	46.2	34.5	27.8	44.7	46.2	19.2	14.3	47.2	34.5	27.8	100.0	**28.4**	**56.9**
Unknown	0.1	0.0	0.0	0.0	0.0	1.1	0.0	0.0	5.6	2.4	2.0	0.0	**0.0**	**0.0**
Atrial fibrillation (%)														
Yes	16.6	11.5	3.2	4.2	16.4	18.2	29.0	28.6	16.7	21.4	1.9	0.0	23.7	23.5
No	83.4	88.5	96.8	95.8	83.0	80.6	71.0	71.4	80.6	71.4	94.4	100.0	76.3	76.5

Supplemental Table B-8a. Differences in patient characteristics between those with and without functional outcome assessment at 1 year after stroke

	Oxford		Joinville		Melbourne		Arcadia		Perth		Matão		Tartu	
Characteristic	Assessed n=910	Unassessed n=78	Assessed n=1708	Unassessed n=161	Assessed n=494	Unassessed n=312	Assessed n=328	Unassessed n=14	Assessed n=36	Unassessed n=84	Assessed n=54	Unassessed n=2	Assessed n=194	Unassessed n=51
Unknown	0.0	0.0	0.0	0.0	0.6	1.1	0.0	0.0	2.8	7.1	3.7	0.0	0.0	0.0
Ischaemic heart disease (%)														
Yes	11.2	12.8	95.8	8.3	**13.0**	**10.5**	15.5	14.3	13.9	8.3	7.4	0.0	29.4	35.3
No	88.7	85.9	4.2	91.7	**87.0**	**88.3**	84.5	85.7	86.1	85.7	88.9	100.0	70.6	64.7
Unknown	0.1	1.3	0.0	0.0	**0.0**	**1.1**	0.0	0.0	0.0	0.0	3.7	0.0	0.0	0.0
Peripheral vascular disease (%)														
Yes	5.6	3.9	-	-	7.3	6.8	8.5	0.0	-	-	7.4	0.0	-	-
No	94.0	96.2			92.7	92.0	91.5	100.0			89.0	100.0		
Unknown	0.4	0.0			0.0	1.1	0.0	0.0			3.7	0.0		
Transient ischaemic attack (%)														
Yes	12.5	10.3	2.2	5.6	**10.5**	**5.7**	16.8	14.3	22.2	10.7	3.7	0.0	8.8	7.8
No	87.4	89.7	97.8	94.4	**89.3**	**93.7**	83.2	85.7	75.0	78.6	92.6	100.0	91.2	92.2
Unknown	0.1	0.0	0.0	0.0	**0.2**	**0.6**	0.0	0.0	2.8	10.7	3.7	0.0	0.0	0.0
Diabetes (%)														
Yes	12.5	21.8	-	-	17.4	16.8	27.7	14.3	19.4	16.7	-	-	-	-
No	87.5	769			82.4	82.9	72.3	85.7	80.6	82.1				
Unknown	0.0	1.3			0.2	0.3	0.0	0.0	0.0	1.2				
Dementia (%)														
Yes	-	-	-	-	4.3	5.1	-	-	-	-	1.9	0.0	-	-
No					74.1	76.4					94.4	100.0		
Unknown					21.7	18.5					3.7	0.0		
Smoking (%)														
Current	**40.1**	**33.3**	31.0	26.4	**36.2**	**28.5**	19.8	14.3	50.0	27.4	61.1	0.0	-	-
Former	**17.6**	**32.1**	23.2	19.4	**14.8**	**19.7**	-	-	111.1	8.3	-	-		
Never	**41.8**	**20.5**	46.3	54.2	**47.4**	**35.6**	80.2	85.7	30.6	41.7	37.0	100.0		
Unknown	**0.6**	**14.1**	0.0	0.0	**1.6**	**16.2**	0.0	0.0	8.3	22.6	1.9	0.0		
Alcohol use (%)														
Non-drinkers	**39.7**	**41.0**	62.9	58.3	**31.4**	**32.5**	87.5	100.0	**22.2**	**28.6**	83.3	100.0	-	-
Not heavy drinkers	**53.7**	**32.1**	30.4	31.9	**58.1**	**37.6**	-	-	**13.9**	**11.9**	-	-		
Heavy drinkers	**29**	**2.6**	6.7	9.7	**4.5**	**5.7**	12.5	0.0	**41.7**	**20.2**	13.0	0.0		
Ex-drinkers	**-**	**-**	-	-	**3.2**	**4.3**	-	-	**11.1**	**3.6**	-	-		
Unknown	**3.7**	**24.4**	0.0	0.0	**2.8**	**19.9**	0.0	0.0	**11.1**	**35.7**	3.7	0.0		
STROKE-RELATED FACTORS														
Hospital admission, yes (%)	81.0	93.6	100.0	100.0	94.7	94.9	92.7	100.0	80.6	86.9	100.0	100.0	**93.8**	**70.6**
Stroke type (%)														
Ischaemic stroke	**87.8**	**56.4**	68.4	83.3	**85.4**	**70.7**	75.9	71.4	77.8	84.5	90.7	100.0	**84.5**	**60.8**
Intracerebral haemorrhage	**4.8**	**16.7**	7.0	5.6	**10.1**	**13.1**	10.4	7.1	2.8	8.3	9.3	0.0	**9.8**	**13.7**
Subarachnoid haemorrhage	**3.1**	**9.0**	5.0	0.0	**0.2**	**11.1**	1.5	0.0	8.3	6.0	0.0	0.0	**0.0**	**0.0**

Supplemental Table B-8a. Differences in patient characteristics between those with and without functional outcome assessment at 1 year after stroke

	Oxford		**Joinville**		**Melbourne**		**Arcadia**		**Perth**		**Matão**		**Tartu**	
Characteristic	Assessed n=910	Unassessed n=78	Assessed n=1708	Unassessed n=161	Assessed n=494	Unassessed n=312	Assessed n=328	Unassessed n=14	Assessed n=36	Unassessed n=84	Assessed n=54	Unassessed n=2	Assessed n=194	Unassessed n=51
Undetermined	**4.3**	**18.0**	19.6	11.1	**4.3**	**5.1**	12.2	21.4	11.1	1.2	0.0	0.0	**5.7**	**25.5**
Stroke severity														
NIHSS, mean (SD)	**3.7 (4.8)**	**4.4 (5.5)**	5.8 (6.4)	5.6 (6.0)	5.2 (5.4)	5.7 (6.8)	-	-	5.9 (6.6)	7.6 (7.2)	6.8 (5.6)	9.0 (5.0)	5.7 (6.5)	7.6 (8.6)
GCS, reversed, mean (SD)	-	-	-	-	-		**3.8 (1.8)**	**3.7 (1.5)**	-	-	-	-	-	-
POST-STROKE FACTORS														
Depression at 1 year														
Yes	-	-	-	-	16.0	0.0	-	-	-	-	-	-	-	-
No					65.6	2.0								
Unknown					18.4	98.0								
Recurrence at 1 year, yes (%)					0.6	0.3					14.8	0.0		

Supplemental Table B-8b. Differences in patient characteristics between those with and without functional outcome assessment at 5 years after stroke

Characteristic	Oxford		Joinville		Melbourne		Porto		Auckland		Tartu	
	Assessed n=385	Unassessed n=18	Assessed n=423	Unassessed n=175	Assessed n=460	Unassessed n=93	Assessed n=259	Unassessed n=22	Assessed n=303	Unassessed n=578	Assessed n=131	Unassessed n=30
SOCIODEMOGRAPHIC												
Female (%)	49.4	66.7	42.1	34.3	49.6	52.3	57.1	63.6	46.2	50.5	51.9	66.7
Age, mean (SD)	69.9 (11.5)	70.8 (15.4)	**58.1 (14.4)**	**62.7 (12.1)**	**69.2 (14.3)**	**60.7 (16.9)**	64.0 (12.6)	67.2 (14.3)	**66.0 (12.6)**	**70.0 (14.2)**	**64.7 (12.5)**	**70.4 (9.1)**
Marital status (%)												
Single/widowed	34.8	33.3	-	-	-	-	-	-	-	-	-	-
Married	56.4	55.6										
Unknown	8.8	11.1										
Education level (%)												
≤ Grade 12	76.6	33.3	92.2	92.5	**9.1**	**35.6**	84.6	68.2	**46.5**	**47.2**	-	-
> Grade 12	12.2	16.7	7.8	6.0	**36.5**	**64.4**	2.7	9.1	**45.9**	**29.6**		
Unknown	11.2	50.0	0.0	1.5	**5.2**	**0.0**	12.7	22.7	**7.6**	**23.2**		
Social class (%)												
Professional	**9.1**	**16.7**	-	-	35.9	27.3	29.0	13.6	**24.1**	**17.0**	-	-
Non-manual	**23.9**	**5.6**			11.3	10.6	57.1	72.7	**20.5**	**18.9**		
Manual	**48.3**	**27.8**			40.4	33.3	7.7	4.6	**38.3**	**33.0**		
Unknown	**18.7**	**50.0**			12.4	28.8	6.2	9.1	**17.2**	**31.1**		
PRE-STROKE HEALTH												
Modified Rankin Score (%)												
0-2	**92.5**	**83.3**	-	-	-	-	95.0	95.5	-	-	**86.3**	**56.7**
3-5	**7.5**	**5.6**					4.6	0.0			**0.8**	**0.0**
Unknown	**0.0**	**11.1**					0.4	4.6			**13.0**	**43.3**
Barthel Index score (%)												
20	-	-	-	-	**68.9**	**37.9**	-	-	-	-	-	-
<20					**10.4**	**4.6**						
Unknown					**20.7**	**57.6**						
Pre-stroke dependence (%)												
Yes	-	-	-	-	-	-	-	-	**94.1**	**88.6**	-	-
No									**5.6**	**8.1**		
Unknown									**0.3**	**3.3**		
MEDICAL HISTORY												
Hypertension (%)												
Yes	59.2	38.9	61.0	70.2	54.8	46.2	66.0	45.5	56.8	52.9	**70.2**	**50.0**
No	40.8	61.1	39.0	29.9	44.8	53.0	34.0	54.6	42.6	44.8	**29.8**	**50.0**
Unknown	0.0	0.0	0.0	0.0	0.4	0.8	0.0	0.0	0.7	2.3	**0.0**	**0.0**
Atrial fibrillation (%)												
Yes	13.3	11.1	0.0	0.0	14.1	9.9	6.2	9.1	14.9	17.1	16.0	20.0
No	86.8	88.9	100.0	100.0	85.4	89.4	93.8	90.9	85.2	81.8	84.0	80.0

Supplemental Table B-8b. Differences in patient characteristics between those with and without functional outcome assessment at 5 years after stroke

Characteristic	Oxford		Joinville		Melbourne		Porto		Auckland		Tartu	
	Assessed n=385	Unassessed n=18	Assessed n=423	Unassessed n=175	Assessed n=460	Unassessed n=93	Assessed n=259	Unassessed n=22	Assessed n=303	Unassessed n=578	Assessed n=131	Unassessed n=30
Unknown	0.0	0.0	0.0	0.0	0.4	0.8	0.0	0.0	0.0	0.4	0.0	0.0
Ischaemic heart disease (%)												
Yes	9.6	5.6	0.0	0.0	10.9	6.1	5.8	4.6	16.5	19.4	28.2	16.7
No	90.1	94.4	100.0	100.0	88.7	93.2	94.2	95.5	83.5	80.3	71.8	83.3
Unknown	0.3	0.0	0.0	0.0	0.4	0.8	0.0	0.0	0.0	0.4	0.0	0.0
Peripheral vascular disease (%)												
Yes	6.0	5.6	-	-	5.2	6.1	4.6	4.6	-	-	-	-
No	94.0	94.4			94.1	93.2	86.1	86.4				
Unknown	0.0	0.0			0.7	0.8	9.3	9.1				
Transient ischaemic attack (%)												
Yes	14.8	16.7	0.0	0.0	8.7	6.1	9.3	22.7	-	-	8.4	10.0
No	85.2	83.3	100.0	100.0	90.9	93.2	90.7	77.3			91.6	90.0
Unknown	0.0	0.0	0.0	0.0	0.4	0.4	0.0	0.0			0.0	0.0
Diabetes (%)												
Yes	9.4	11.1	-	-	18.4	12.2	-	-	-	-	-	-
No	90.7	83.3			81.5	87.9						
Unknown	0.0	5.6			0.4	0.0						
Dementia (%)												
Yes	-	-	-	-	2.0	2.3	-	-	0.3	0.4	-	-
No					77.6	80.3			99.7	98.9		
Unknown					20.4	17.4			0.0	0.9		
Smoking (%)												
Current	**38.2**	**38.9**	27.9	31.3	**34.4**	**23.5**	10.8	13.6	**40.6**	**39.5**	-	-
Former	**21.3**	**16.7**	24.4	20.9	**15.0**	**31.1**	-	-	**49.5**	**36.5**		
Never	**40.3**	**38.9**	47.8	47.8	**45.4**	**35.6**	74.9	68.2	**9.6**	**17.3**		
Unknown	**0.3**	**5.6**	0.0	0.0	**5.2**	**9.9**	14.3	18.2	**0.3**	**6.8**		
Alcohol use (%)												
Non-drinkers	**37.9**	**50.0**	52.7	44.8	32.0	32.6	48.3	50.0	**28.1**	**32.0**	-	-
Not heavy drinkers	**55.1**	**33.3**	38.3	43.3	52.2	44.7	-	-	**58.4**	**43.8**		
Heavy drinkers	**4.4**	**0.0**	9.0	11.9	5.4	5.3	45.6	40.9	**12.5**	**13.7**		
Ex-drinkers	-	-	-	-	3.5	3.0	-	-	-	-		
Unknown	**2.6**	**16.7**	0.0	0.0	7.0	14.4	6.2	9.1	**1.0**	**10.6**		
STROKE-RELATED FACTORS												
Hospital admission, yes (%)	**63.9**	**94.4**	100.0	100.0	93.9	97.7	96.5	100.0	96.0	95.3	**93.9**	**63.3**
Stroke type (%)												
Ischaemic stroke	**88.6**	**38.9**	70.9	82.1	83.9	59.9	78.8	81.8	79.2	81.5	84.7	53.3
Intracerebral haemorrhage	**4.2**	**22.2**	8.0	6.0	12.6	9.1	14.3	9.1	10.2	9.3	10.7	13.3

Supplemental Table B-8b. Differences in patient characteristics between those with and without functional outcome assessment at 5 years after stroke

Characteristic	Oxford		Joinville		Melbourne		Porto		Auckland		Tartu	
	Assessed n=385	Unassessed n=18	Assessed n=423	Unassessed n=175	Assessed n=460	Unassessed n=93	Assessed n=259	Unassessed n=22	Assessed n=303	Unassessed n=578	Assessed n=131	Unassessed n=30
Subarachnoid haemorrhage	**4.4**	**27.8**	5.9	3.0	0.0	29.6	3.5	9.1	6.3	4.2	-	-
Undetermined	**2.9**	**11.1**	15.1	9.0	3.5	1.5	3.5	0.0	4.3	5.0	4.6	33.3
Stroke severity												
NIHSS, mean (SD)	3.3 (4.5)	3.2 (3.6)	5.8 (6.5)	5.0 (5.0)	4.2 (4.4)	5.2 (6.0)	-	-	-	-	5.4 (6.6)	7.4 (8.0)
UNSS, reversed, mean (SD)	-	-	-	-	-	-	7.3 (7.8)	6.8 (7.3)	-	-	-	-
GCS, reversed, mean (SD)	-	-	-	-	-	-	-	-	1.7 (1.8)	1.7 (1.9)	-	-
POST-STROKE FACTORS												
Depression at 5 years (%)												
Yes	-	-	-	-	**12.8**	**0.8**	-	-	**48.8**	**2.4**	-	-
No					**74.6**	**0.8**			**31.7**	**1.4**		
Unknown					**12.6**	**98.5**			**19.5**	**96.2**		
Recurrence at 5 years, yes (%)					9.1	3.8						

Supplemental Table B-9. Comparison of complete-case analysis and sensitivity analyses of missing data on relative risk of functional outcome between women and men at 1 year and 5 years after stroke

Study	Unadjusted				Adjusted					
	Complete-case	Imputed*	Replace with extreme value of 0	Replace with extreme value of 1	Complete-case	Imputed*		Replace with extreme value of 0	Replace with extreme value of 1	
	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)	MRR	(95% CI)	MRR (95% CI)	MRR	(95% CI)
Melbourne										
1-year	**1.45 (1.18-1.79)**	**1.42 (1.16-1.74)**	**1.40 (1.10-1.77)**	**1.21 (1.08-1.35)**	**1.25 (1.04-1.50)**	**1.30**	**(1.07-1.59)**	1.22 (0.97-1.53)	**1.12**	**(1.01-1.25)**
5-year	1.22 (0.99-1.51)	**1.29 (1.01-1.66)**	1.20 (0.94-1.51)	1.15 (0.99-1.34)	1.02 (0.84-1.45)	1.09	(0.86-1.39)	1.00 (0.80-1.24)	1.04	(0.90-1.20)
Joinville										
5-year	1.20 (0.78-1.83)	1.14 (0.78-1.66)	1.19 (0.77-1.85)	1.05 (0.87-1.27)	1.06 (0.71-1.57)	1.00	(0.96-1.09)	1.02 (0.67-1.55)	1.00	(0.83-1.20)
Perth										
1-year	**6.80 (1.80-25.66)**	**2.14 (0.84-5.46)**	**7.19 (1.72-29.9)**	**1.28 (1.09-1.51)**	**5.10 (1.33-19.58)**	1.91	(0.71-5.15)	1.76 (0.29-3.23)	**1.21**	**(1.04-1.41)**
Tartu										
1-year	1.21 (0.81-1.83)	1.10 (0.80-1.51)	1.14 (0.83-1.55)	1.22 (0.80-1.86)	0.89 (0.60-1.32)	0.89	(0.65-1.21)	0.92 (0.68-1.24)	0.92	(0.61-1.40)
Auckland										
5-year	1.25 (0.86-1.80)	**1.17 (1.08-1.27)**	1.14 (0.76-1.72)	1.07 (0.99-1.16)	0.99 (0.69-1.41)	1.00	(0.93-1.08)	0.99 (0.66-1.50)	1.02	(0.95-1.11)
Pooled data										
1-year (10 studies)	**1.32 (1.18-1.48)**	**1.31 (1.20-1.43)**	**1.29 (1.14-1.46)**	**1.18 (1.05-1.32)**	1.08 (0.97-1.20)	1.08	(0.98-1.18)	1.05 (0.93-1.18)	1.03	(0.97-1.10)
5-year (7 studies)	**1.31 (1.16-1.47)**	**1.26 (1.13-1.40)**	**1.31 (1.18, 1.46)**	**1.27 (1.19-1.35)**	1.05 (0.94-1.18)	1.02	(0.96-1.09)	1.07 (0.97-1.19)	**1.10**	**(1.03-1.17)**

Bold denotes statistically significant results between women and men.

RR (95% CI), relative risk (95% confidence interval)

*using multiple imputation assuming missing at random as described in Supplementary 3 (Supplementary methods)

Supplemental Table B-10. List of covariates not meeting the criteria for factors confounding the difference in 5-year functional outcome between women and men

Study ID	Covariates not meeting the criteria for confounding factors in univariable model	Confounding factors in univariable model that were not significant in the final multivariable model
Oxford	SEP, education, hypertension, AF, IHD, PVD, TIA, diabetes, BMI, smoking, alcohol, hospital admission, stroke type, severity NIHSS*, recurrence	
Joinville	Race, hypertension, age*, stroke severity (NIHSS)*, AF, IHD, PVD, TIA, BMI, smoking, alcohol, hospital admission, stroke type, pre-stroke medication (antihypertensives, antiplatelet, anticoagulant), delay to hospital	
Melbourne	Race, SEP, education, hypertension, IHD, PVD, TIA, diabetes, smoking, alcohol, stroke type, hospital admission, pre-stroke medication (antiplatelet, anticoagulant, antihypertensives), onset LOC, onset hemiplegia, onset incontinence, depression (1-year), depression (5-year), IDA score (overall and sub-dimension: anxiety, depression), recurrence (1-year), recurrence (5-year)	Pre-stroke Barthel*, institutional residence
Martinique	Hypertension, AF, IHD, PVD, TIA, BMI, smoking, alcohol, stroke type, hospital admission, delay to hospital	
Porto	SEP, education, hypertension, AF, IHD, PVD, TIA, BMI, alcohol, stroke type, stroke severity (UNSS), hospital admission, delay to hospital, onset hemiplegia, onset LOC*, pre-stroke Rankin*, recurrence	
Auckland	SEP, education, hypertension, IHD, dementia, BMI, alcohol, smoking, pre-stroke medication (antihypertensives, antiplatelet, anticoagulant), stroke type, hospital admission, delay to hospital, onset hemiplegia, marital status, onset LOC, severity GCS*, depression (5-year), GHQ-28 scores (overall and sub-dimension: somatic, social, anxiety and depression)	
Tartu	Hypertension, AF, IHD, TIA, hospital admission, stroke type, delay to hospital, pre-stroke medication (antihypertensives, antiplatelet), severity NIHSS*, pre-stroke mRS*	

AF, Atrial fibrillation; BMI, body mass index; GCS, Glasgow Coma Scale; IHD, ischaemic heart disease; IDA, Irritability-Depression-Anxiety Scale; GHQ-28, 28-item General Health Questionnaire; LOC, loss of consciousness (at onset); mRS, modified Rankin scale; NIH, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease, TIA, transient ischaemic attack; UNSS, Unified Neurological Stroke Scale; SEP, socioeconomic position

* not meeting criteria of being a confounder but remain in the final model

Supplemental Table B-11. Heterogeneity analyses in functional outcome at 5 years among seven population-based studies

		No of studies	No of poorer outcome (n/N)		Unadjusted				Adjusted*			
			Men	Women	I^2 (%)	P^H	RR(95% CI)	$P^{sub-group}$	I^2 (%)	P^H	RR(95% CI)	$P^{sub-group}$
Study-level characteristics												
Geographic region	Australasia	2	140/395	169/368	0.0	0.935	1.23 (1.02-1.48)	0.702	0.0	0.865	1.01 (0.85-1.20)	0.866
	Europe	3	116/369	186/406	43.9	0.168	1.45 (1.11-1.88)		0.0	0.417	1.11 (0.93-1.34)	
	Caribbean	1	48/150	42/115	NA	1.000	1.17 (0.77-1.78)		NA	1.000	0.98 (0.67-1.42)	
	South America	1	38/245	33/178	NA	1.000	1.20 (0.78-1.83)		NA	1.000	1.06 (0.71-1.57)	
Income group	HIC	5	256/764	355/774	20.4	0.285	1.34 (1.15-1.56)	0.516	0.0	0.675	1.06 (0.94-1.20)	0.786
	LMIC†	2	86/395	75/293	0.0	0.941	1.18 (0.88-1.59)		0.0	0.785	1.01 (0.77-1.33)	
Loss to follow-up	≤20%	6	302/996	386/927	8.6	0.361	1.31 (1.15-1.50)	0.807	0.0	0.799	1.06 (0.94-1.19)	0.727
	>20%	1	40/163	44/140	NA	1.000	1.25 (0.86-1.80)		NA	1.000	0.99 (0.69-1.41)	
Functional outcome measurement	Barthel Index	1	100/232	125/228	NA	1.000	1.22 (0.99-1.51)	0.581	NA	1.000	1.02 (0.84-1.24)	0.734
	mRS	6	242/927	305/893	0.3	0.414	1.35 (1.16-1.56)		0.0	0.798	1.07 (0.93-1.23)	
Age difference‡	≤4.5 years	6	327/1096	401/999	0.0	0.540	1.28 (1.14-1.45)	0.282	0.0	0.980	1.03 (0.92-1.16)	0.245
	>4.5 years	1	15/63	29/68	NA	1.000	1.79 (1.06-3.02)		NA	1.000	1.48 (0.88-2.51)	
Severity instrument	NIHSS	3	198/672	252/596	31.9	0.230	1.35 (1.11-1.64)	0.842	0.0	0.823	1.06 (0.92-1.22)	0.926
	Barthel at onset	1	48/150	42/115	NA	1.000	1.17 (0.77-1.78)		NA	1.000	0.98 (0.67-1.42)	
	Others§	3	96/337	136/356	6.1	0.345	1.27 (1.02-1.59)		0.0	0.379	1.06 (0.85-1.31)	
Pre-stroke function	Unavailable	2	86/395	75/293	0.0	0.941	1.18 (0.88-1.59)	0.516	0.0	0.785	1.01 (0.77-1.33)	0.786
	Available	5	256/764	355/774	20.4	0.285	1.34 (1.15-1.56)		0.0	0.675	1.06 (0.94-1.20)	
Time to follow-up	5 years	5	286/985	338/851	0.0	0.492	1.31 (1.15-1.50)	0.957	0.0	0.958	1.04 (0.92-1.18)	0.746
	Not 5 years‖	2	56/174	92/216	52.7	0.146	1.36 (0.88-2.09)		42.0	0.189	1.14 (0.78-1.68)	

P^H, P-value of heterogeneity; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; RR (95% CI), Relative risk (95% confidence interval) between women and men; HIC, High-income country; LMIC, Low- and middle-income countries

* RR adjusted for actual confounders

† low- and middle-income country group (LMIC) included studies conducted in Martinique

‡ indicates difference in median age at onset between women and men

§ other instruments including Glasgow coma scale and loss of consciousness

‖ the follow-up time occurred at 7 years (Porto) or 4 years (Tartu) after stroke

Supplemental Table B-12. Prevalence of admission and discharge medication, in-hospital investigation by female sex from 10 studies among cases assessed at 1 year

	Oxford		Joinville		Melbourne		Arcadia		Perth		Orebro		Martinique		Porto		Matão		Tartu	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Admission medication (%)																				
Antihypertensive	-	-	-	-	51.5	58.4	-	-	33.3	57.1‡	-	-	-	-	-	-	-	-	-	-
Antiplatelet	-	-	-	-	32.9	32.9	28.4	32.0	20.0	35.7‡	-	-	-	-	-	-	-	-	-	-
Anticoagulation	-	-	-	-	4.6	4.8	11.3	18.8	13.3	0.0‡	-	-	-	-	-	-	-	-	-	-
Thrombolysis*	-	-	9.5	8.8	0.0	0.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Discharge medication (%)																				
Antihypertensive	-	-	-	-	45.6	48.5	-	-	53.3	64.3‡	-	-	-	-	49.3	54.1	-	-	-	-
Antiplatelet*	-	-	-	-	56.8	60.5	-	-	45.5	76.9‡	-	-	-	-	70.4	69.8	-	-	-	-
Anticoagulation*	-	-	-	-	21.4	16.1	-	-	**45·5**	**0·0**‡	-	-	-	-	-	-	-	-	-	-
Investigation (%)																				
Neuroimaging	-	-	100.0	100.0	97.1	95.3	90.3	90.6	86.7	100.0‡	97.5	95.0	98.4	99.4	99.0	99.6	100.0	100.0	100.0	96.6
Carotid investigation*	-	-	84.8	85.9	60.0	59.1	35.6	27.5	27.3	0.0‡	-	-	-	-	52.6	52.9	-	-	**34·1**	**14·9**
Echocardiography*	-	-	-	-	**50·6**	**36·4**	24.4	15.7	36.4	7.7‡	-	-	-	-	48.9	45.9	-	-	-	-
Surgery intervention (%)																				
Carotid endarterectomy*	7.6	4.2	-	-	1.9	1.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Coiling/clipping/other†	0.0	2.6‡	-	-	0.0	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Bold numbers denote p-value <0.05; $\chi 2$ test or Fisher's exact test, as appropriate, was used to examine if there were sex differences in admission medication and discharge medication, in-hospital investigation and surgical interventions.

* among ischaemic stroke only

† haemorrhagic stroke

‡ Fisher's Exact test

Supplemental Table B-13. Prevalence of admission and discharge medication, in-hospital investigation by sex from 7 studies among cases assessed at 5 years

	Oxford		Joinville		Melbourne		Martinique		Porto		Auckland		Tartu	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Admission medication (%)														
Antihypertensive	-	-	-	-	48.1	53.7	-	-	-	-	-	-	-	-
Antiplatelet	-	-	-	-	28.0	30.2	-	-	-	-	-	-	-	-
Anticoagulation	-	-	-	-	5.1	6.5	-	-	-	-	-	-	-	-
Thrombolysis*	-	-	10.1	9.8	0.0	1.6	-	-	-	-	0.8	0.6	-	-
Discharge medication (%)														
Antihypertensive	-	-	-	-	48.6	48.6	-	-	46.3	55.6	60.6	62.9	-	-
Antiplatelet*	-	-	-	-	60.3	60.5	-	-	63.5	69.0	79.9	81.7	-	-
Anticoagulation*	-	-	-	-	20.7	19.5	-	-	-	-	15.9	13.8	-	-
Investigation (%)														
Neuroimaging	-	-	100.0	100.0	96.3	96.3	98.5	100.0	98.2	99.3	93.9	92.3	100.0	96.9
Carotid investigation*	-	-	73.0	82.0	62.0	63.0	-	-	56.7	59.5	5.2	3.1	**54·9**	**21·4**
Echocardiography*	-	-	-	-	**52·7**	**41·4**	-	-	60.3	61.9	**1·4**	**0·0**‡	-	-
Surgery intervention (%)														
Carotid endarterectomy*	7.1	8.5	-	-	**3·4**	**0·5**	-	-	-	-	-	-	-	-
Coiling/clipping/other†	0.0	5.3‡	-	-	25.0	0.0	-	-	-	-	13.7	18.5	-	-

Bold numbers denote p-value <0.05; $\chi 2$ test or Fisher's exact test, as appropriate, was used to examine whether there were sex differences in admission medication and discharge medication, in-hospital investigation and surgical interventions.

* among ischaemic stroke only

† haemorrhagic stroke

‡ Fisher's Exact test

Supplemental Table B-14. List of covariates not meeting the criteria for factors confounding the difference in 5-year Participation restriction between women and men

Study ID	Covariates not meeting the criteria for confounding factors in univariable model	Confounding factors in univariable model that were not significant in the final multivariable model
Melbourne	Race, SEP, education, hypertension, IHD, PVD, TIA, diabetes, alcohol, hospital admission, recurrence, institutional residence, pre-stroke medication (antihypertensives, antiplatelet, anticoagulant), onset LOC, onset incontinence, onset hemiplegia, depression (1-year), depression (5-year), IDA overall score, recurrence (1-year), recurrence (5-year)	Smoking, institutional residence, IDA sub-dimension score of anxiety
Auckland	Ethnicity, SEP, education, hypertension, IHD, dementia, BMI, smoking, alcohol, pre-stroke medication (antihypertensives, antiplatelet, anticoagulant), hospital admission, delay to hospital, marital status, onset LOC, onset hemiplegia, GCS*, depression (5-year), GHQ-28 scores (overall and sub-dimension: somatic, social, anxiety and depression)	

AF, Atrial fibrillation; BMI, body mass index; GCS, Glasgow Coma Scale; IHD, ischaemic heart disease; IDA, Irritability-Depression-Anxiety Scale; GHQ-28, 28-item General Health Questionnaire; LOC, loss of consciousness (at onset); mRS, modified Rankin scale; PVD, peripheral vascular disease, TIA, transient ischaemic attack; SEP, socioeconomic position

* not meeting criteria of being a confounder but remaining in the final model

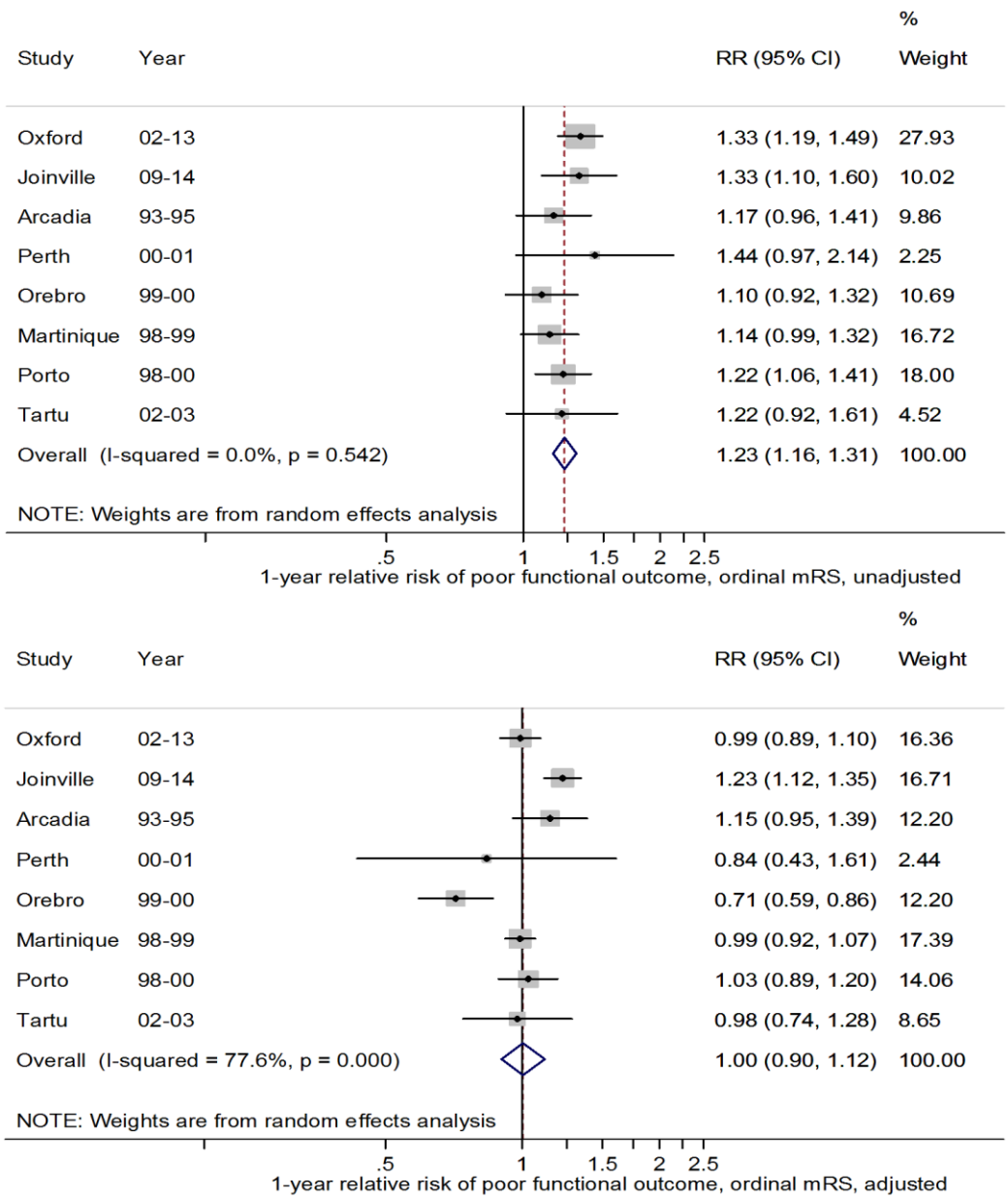
Supplemental Table B-15. Comparison of complete-case analysis and imputed analysis of London handicap scores between women and men at 5 years after stroke

Study	Unadjusted		Adjusted for confounders	
	Complete-case MD (95% CI)	**Imputed*** MD (95% CI)	**Complete-case** MD (95% CI)	**Imputed*** MD (95% CI)
Melbourne	**-6.89 (-10.71, -3.07)**	**-7.06 (-11.0, -3.13)**	-2.74 (-5.95, 0.47)	-2.51 (-6.24, 1.21)
Auckland	-3.89 (-8.16, 0.37)	-4.21 (-8.79, 0.37)	-2.05 (-6.12, 2.01)	-1.78 (-6.51, 2.94)
Pooled (2 studies)	**(-8.47, -5.55 2.63)**	**-5.60 (-8.72, -2.47)**	-2.48 (-4.99, 0.03)	-2.22 (9-5.15, 0.71)

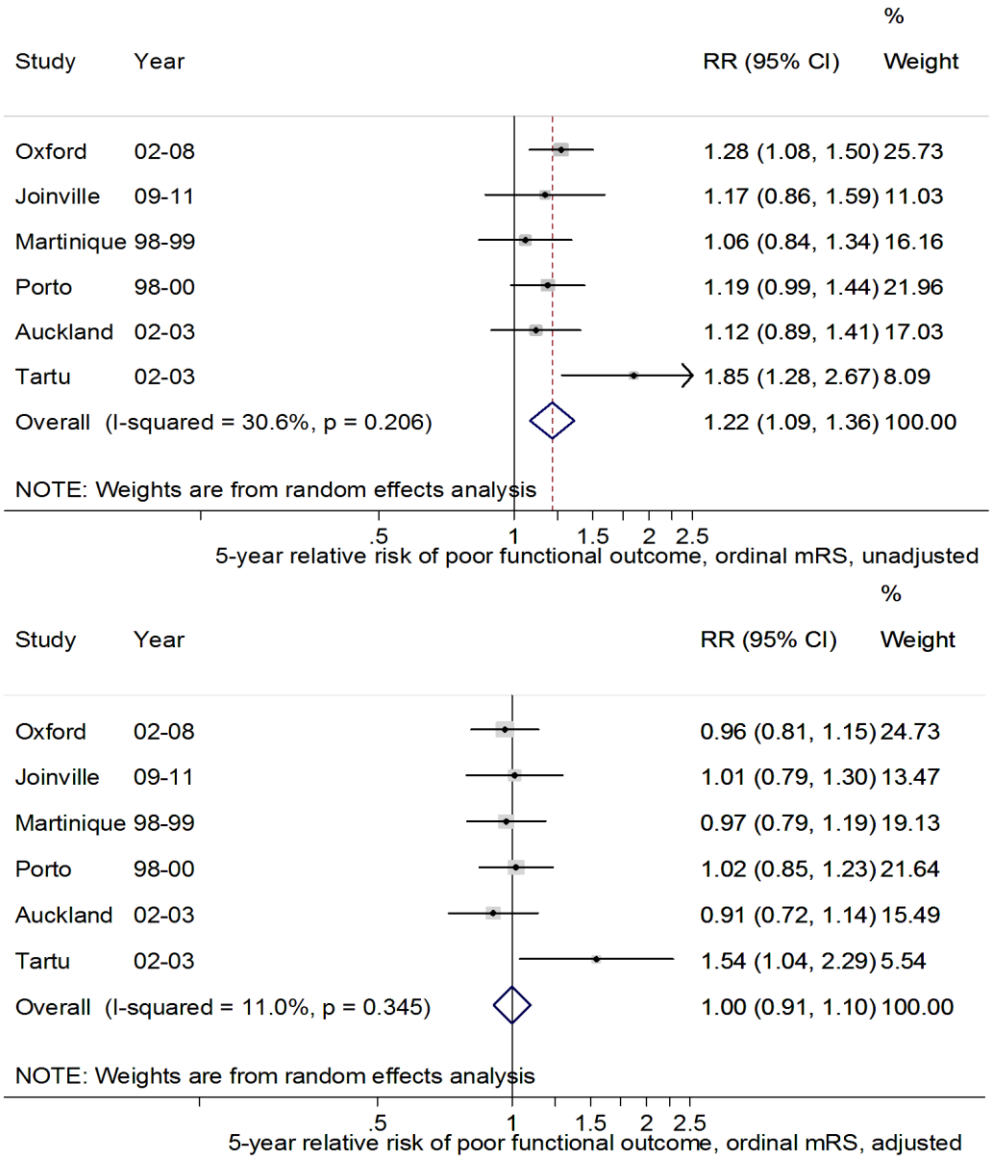
Bold denotes statistically significant results between women and men.
MD (95% CI), mean difference (95% confidence interval)
*using multiple imputation as described in supplementary methods

Supplemental Table B-16. Distribution of scores on each sub-dimension of the London Handicap Scale at 5 years after stroke, by sex, in Melbourne and Auckland. Higher categories (3-6) denotes more severe participation restriction.

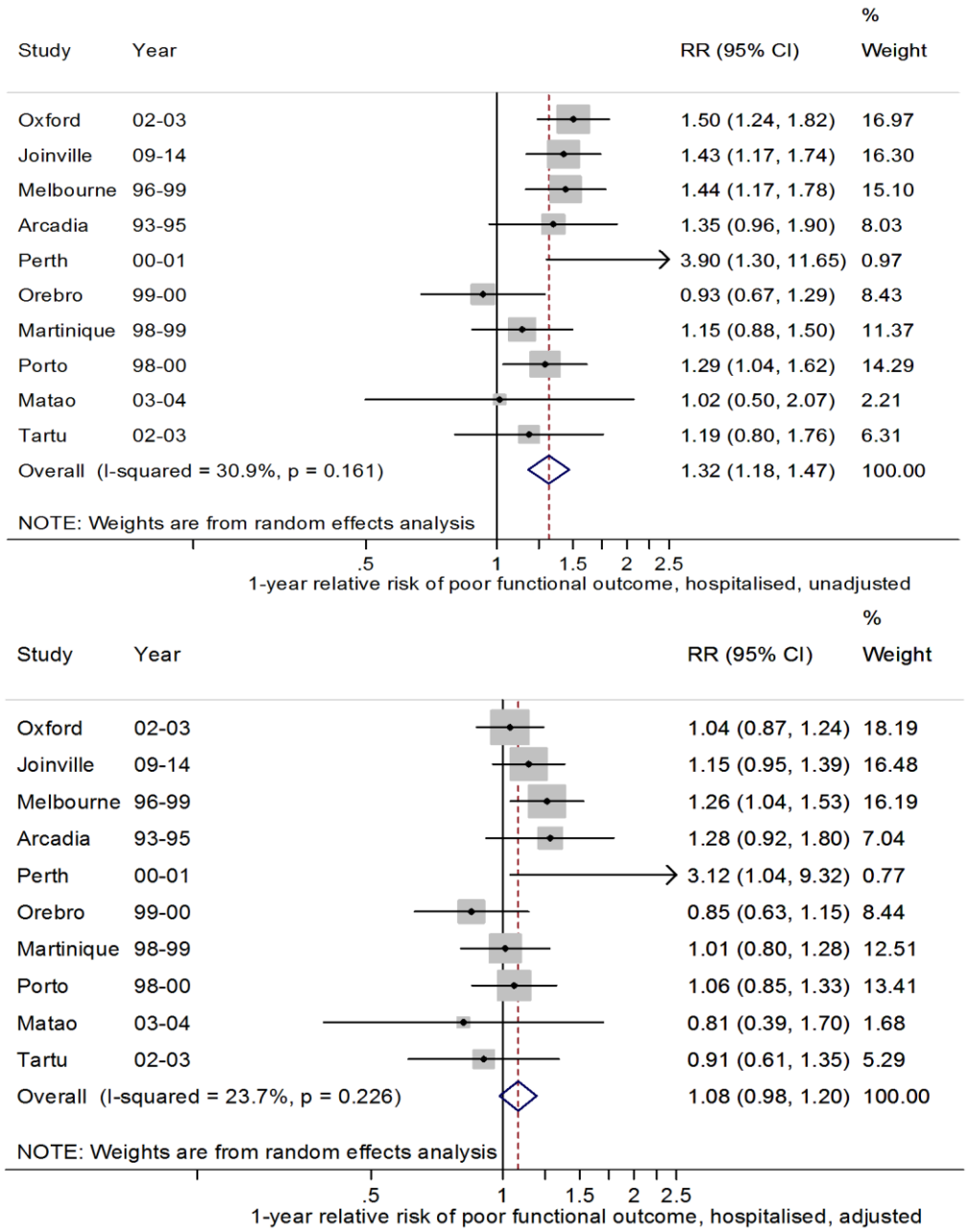
	Melbourne					**Auckland**				
	Men		Women		p	Men		Women		p
	n	%	n	%		n	%	n	%	
Mobility										
Less disadvantage (1-2)	116	65.9	90	51.4	**0.006**	114	79.2	82	67.2	**0.027**
Disadvantage (3-6)	60	34.1	85	48.6		30	20.8	40	32.8	
Physical										
Less disadvantage (1-2)	117	66.5	93	53.1	**0.011**	110	76.4	72	59.0	**0.002**
Disadvantage (3-6)	59	33.5	82	46.9		34	23.6	5	41.0	
Occupation										
Less disadvantage (1-2)	102	58.0	78	44.6	**0.012**	86	59.7	55	45.1	**0.017**
Disadvantage (3-6)	74	42.1	97	55.4		58	40.3	67	54.9	
Social										
Less disadvantage (1-2)	156	88.6	138	78.9	**0.013**	123	85.4	101	82.8	0.558
Disadvantage (3-6)	20	11.4	37	21.1		21	14.6	21	17.2	
Orientation										
Less disadvantage (1-2)	157	89.2	134	76.6	**0.002**	120	83.3	96	78.7	0.334
Disadvantage (3-6)	19	10.8	41	23.4		24	16.7	26	21.3	
Economic										
Less disadvantage (1-2)	131	74.4	124	70.9	0.453	95	66.0	98	80.3	**0.009**
Disadvantage (3-6)	45	25.6	51	29.1		49	34.0	24	19.7	



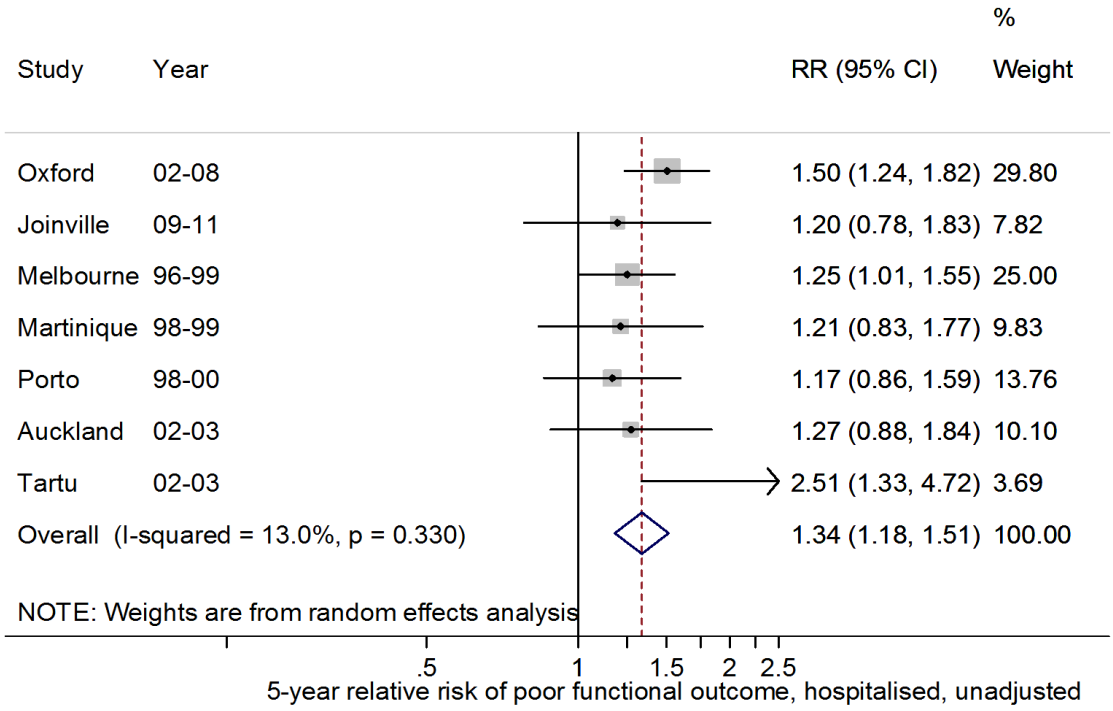
Supplemental Figure B-1. Sensitivity analysis of ordinal regression of Modified Rankin scale (mRS) which were categorised as ordinal outcomes with 3 levels (0-1; 2-3 and 4-5). Relative risk (RR) of poor functional outcome at 1 year after stroke for women compared to men in unadjusted (top panel) and adjusted (bottom panel) analyses among 8 studies combined using random effects meta-analysis.

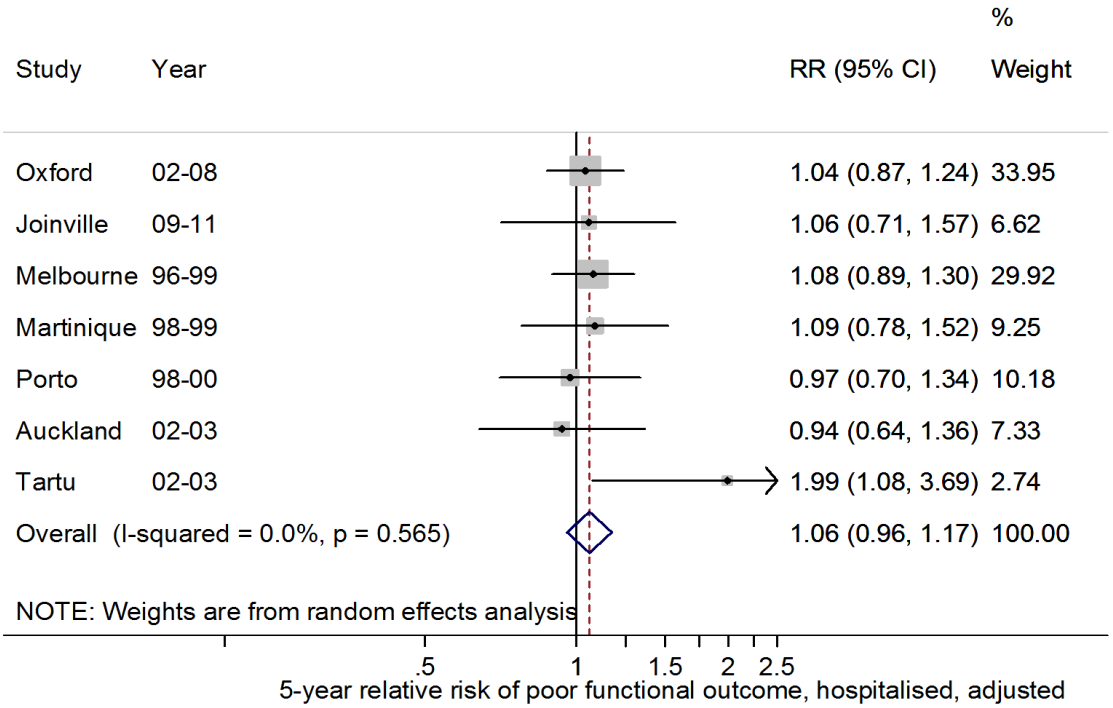


Supplemental Figure B-2. Sensitivity analysis of ordinal regression of Modified Rankin scale (mRS) which were categorised as ordinal outcomes with 3 levels (0-1; 2-3 and 4-5). Relative risk (RR) of poor functional outcome at 1 year after stroke for women compared to men in unadjusted (top panel) and adjusted (bottom panel) analyses among 6 studies combined using random effects meta-analysis.

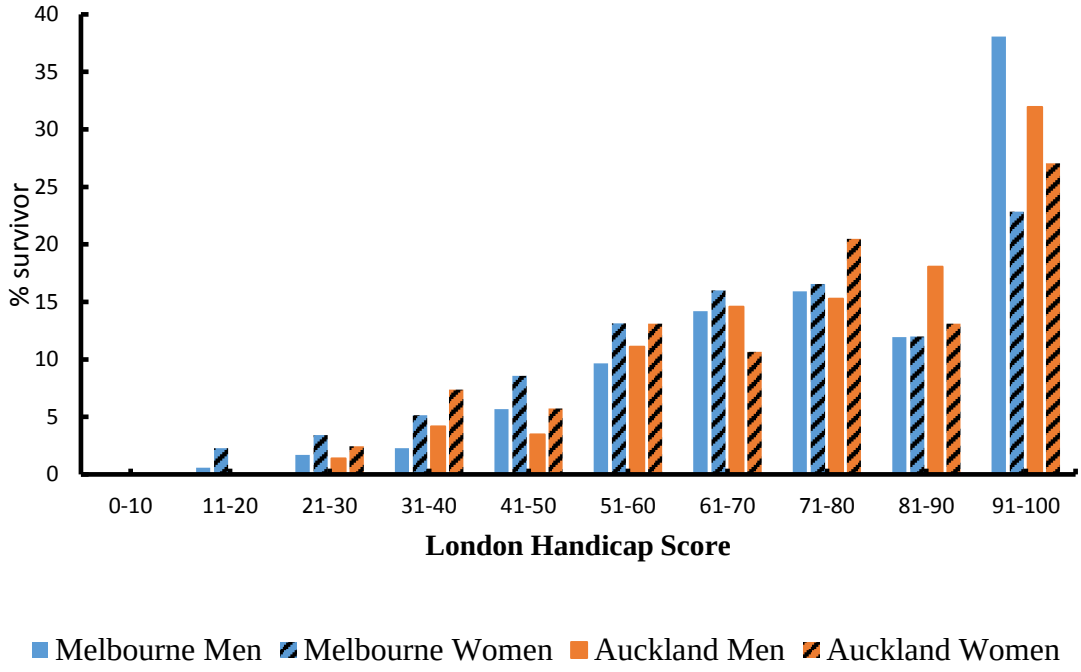


Supplemental Figure B-3. Hospitalised analysis of relative risk (RR) of poor functional outcome at 1 year after stroke for women compared to men in unadjusted (top panel) and adjusted (bottom panel) models in ten studies. Of note, poor outcome was defined as mRS>2 or Barthel Index <20 (Melbourne) or <100 (Matão).

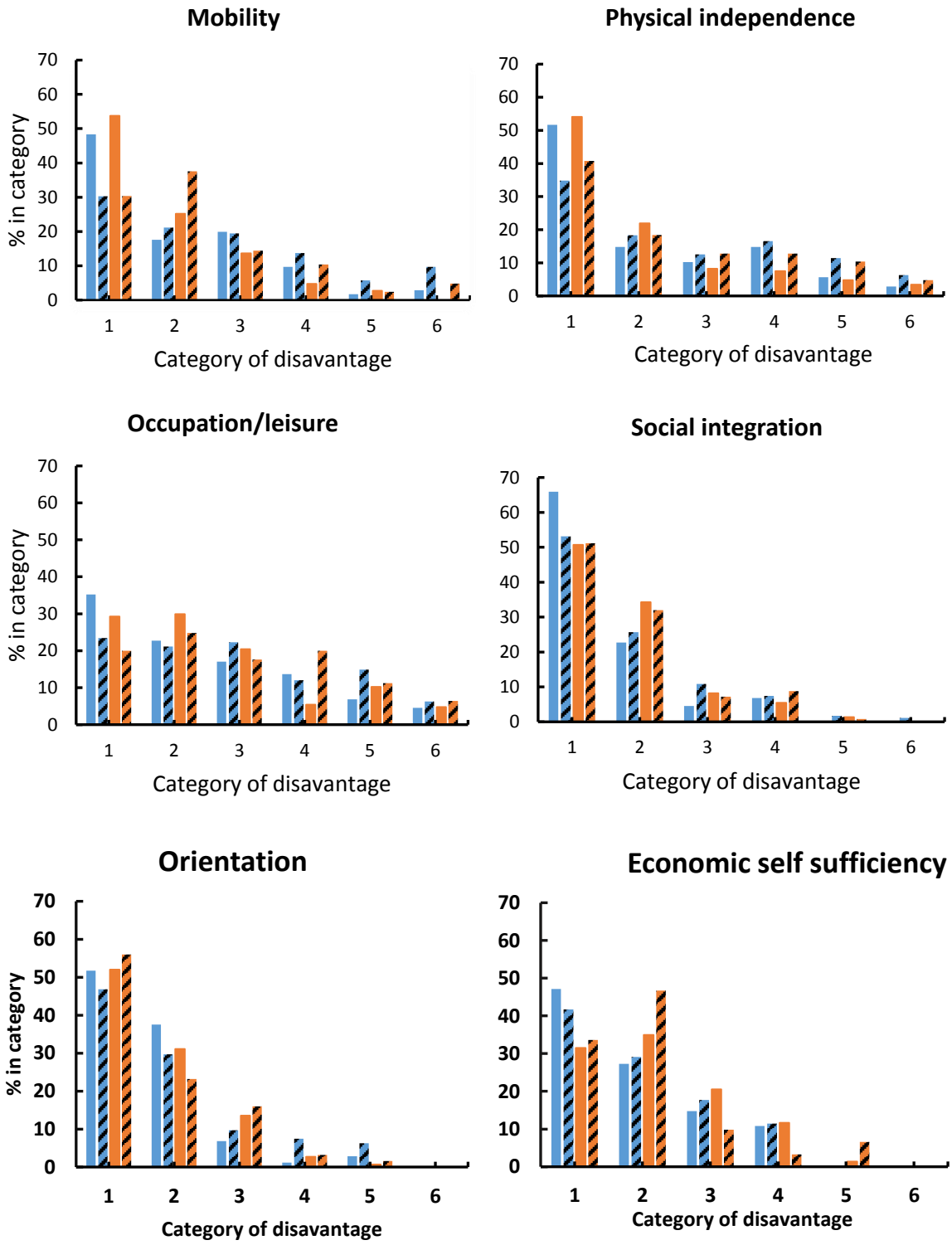




Supplemental Figure B-4: Hospitalised analysis of relative risk (RR) of poor functional outcome at 5 years after stroke for women compared to men in unadjusted (top panel) and adjusted (bottom panel) models in ten studies. Of note, poor outcome was defined as mRS>2 or Barthel Index <20 (Melbourne).



Supplemental Figure B-5. Proportion of 5-year survivors in 10-point interval scores of London Handicap Scale in Melbourne data (blue) and Auckland data (orange). Higher score denotes less participation restriction.



Supplemental Figure B-6. Distribution of scores on each sub-dimension of the London Handicap Scale at 5 years after stroke in Melbourne data (blue) and in Auckland data (orange). Higher categories denotes more severe participation restriction.

Appendix C: Sex differences in long-term health-related quality of life after stroke in the INternational STroke oUtComes sTudy

Supplemental Table C-1. Baseline characteristics by sex and outcomes of survivors at 1 year after stroke with HRQoL assessment among studies conducted in Oxford, Melbourne and Perth

Characteristic	Oxford			Melbourne			Perth		
	Men (n=384)	Women (n=328)	p-value	Men (n=236)	Women (n=229)	p-value	Men (n=16)	Women (n=17)	p-value
SOCIODEMOGRAPHIC									
Age, mean (SD)	70.1 (12.2)	72.7 (12.7)	**0.006**	70.6 (12.5)	73.4 (14.4)	**0.026**	64.1 (4.1)	75.5 (2.5)	**0.024**
Race (%)									
Caucasian	-	-	-	95.3	96.9	0.599	-	-	-
Non-Caucasian				2.2	1.8				
Unknown				2.5	1.3				
Marital status (%)									
Single/widowed	20.3	48.5	**<0.001**	-	-	-	37.5	52.9	0.373
Married	74.2	47.9					62.5	47.1	
Unknown	5.5	3.7					0.0	0.0	
Education level (%)									
≤ Grade 12	73.2	80.2	0.091	66.1	78.2	**0.049**	-	-	-
> Grade 12	19.3	14.3		25.9	19.7				
Unknown	7.6	5.5		8.1	2.2				
Social class (%)									
Professional	20.1	8.2	**<0.001**	35.2	34.5	0.988	25.0	17.6	0.566
Non-manual	23.7	39.6		14.0	14.4		12.5	23.5	
Manual	45.6	39.6		47.9	47.6		56.3	41.2	
Unknown	10.7	12.5		3.0	3.5		6.3	17.7	
PRE-STROKE HEALTH									
Institutional residence (%)									
Yes	-	-	-	4.3	7.4	0.199	0.0	23.5	**0.038**
No				95.8	92.1		100.0	76.5	
Unknown				0.0	0.4		0.0	0.0	
Modified Rankin Score (%)									
0-2	93.8	86.6	**0.005**	-	-	-	93.8	58.8	**0.011**
3-5	6.0	13.1					0.0	41.2	
Unknown	0.3	0.3					6.3	0.0	
Barthel Index score (%)									
20	-	-	-	84.3	75.1	**0.047**	-	-	-
<20				12.7	20.1				
Unknown				3.0	4.8				
MEDICAL HISTORY									
Hypertension (%)									
Yes	58.9	62.8	0.382	51.3	58.1	0.140	37.5	58.8	0.221
No	40.9	37.2		48.7	41.9		62.5	41.2	
Unknown	0.3	0.0		0.0	0.0				
Atrial fibrillation (%)									
Yes	15.4	15.6	0.946	16.5	16.2	0.228	12.5	17.6	0.680
No	84.6	84.5		82.2	83.8		87.5	82.4	
Unknown	0.0	0.0		1.3	0.0		0.0	0.0	
Ischaemic heart disease (%)									
Yes	14.6	7.9	**0.013**	16.1	10.0	0.053	25.0	5.9	0.126
No	85.2	92.1		83.9	90.0		75.0	94.1	
Unknown	0.3	0.0		0.0	0.0		0.0	0.0	

Supplemental Table C-1. Baseline characteristics by sex and outcomes of survivors at 1 year after stroke with HRQoL assessment among studies conducted in Oxford, Melbourne and Perth

Characteristic	Oxford			Melbourne			Perth		
	Men (n=384)	Women (n=328)	p-value	Men (n=236)	Women (n=229)	p-value	Men (n=16)	Women (n=17)	p-value
Peripheral vascular disease (%)									
Yes	5.7	3.7	0.181	10.2	4.8	**0.028**	-	-	-
No	93.8	96.3		89.8	95.2				
Unknown	0.5	0.0		0.0	0.0				
Transient ischaemic attack (%)									
Yes	13.8	12.2	0.526	9.8	10.9	0.568	31.3	88.2	0.196
No	86.2	87.8		89.8	89.1		62.5	11.8	
Unknown	0.0	0.0		0.4	0.0		6.3	0.0	
Diabetes (%)									
Yes	14.1	10.7	0.173	19.1	16.2	0.430	18.8	23.5	0.737
No	85.9	89.3		80.5	83.8		81.3	76.5	
Unknown	0.0	0.0		0.4	0.0		0.0	0.0	
Dementia (%)									
Yes	-	-	-	2.1	5.7	**0.044**	19.1	19.1	1.000
No				76.3	72.1		80.1	80.1	
Unknown				21.6	22.3		0.0	0.0	
Smoking (%)									
Current	51.8	26.8	**<0.001**	51.3	21.4	**<0.001**	68.8	35.3	**0.008**
Former	18.2	17.4		14.8	14.0		18.8	5.9	
Never	29.7	55.2		33.1	62.9		0.0	52.9	
Unknown	0.3	0.6		0.9	1.8		12.5	5.9	
Alcohol use (%)									
Non-drinkers	23.7	53.7	**<0.001**	19.9	44.5	**<0.001**	18.8	29.4	0.132
Not heavy drinkers	71.1	42.4		65.3	50.2		0.0	23.5	
Heavy drinkers	3.7	2.1		7.2	1.3		56.3	35.3	
Ex-drinkers	-	-		5.9	0.4		12.5	0.0	
Unknown	1.6	1.8		1.7	3.5		12.5	11.8	
Pre-stroke medication									
Antihypertensives (%)									
Yes	-	-	-	52.4	57.1	0.327	25.0	47.1	0.212
No				47.6	42.9		75.0	47.1	
Unknown				0.0	0.0		0.0	4.8	
Antiplatelet (%)									
Yes	-	-	-	34.5	33.5	0.831	25.0	47.1	0.441
No				65.5	66.5		68.8	47.1	
Unknown				0.0	0.0		6.3	4.8	
STROKE-RELATED FACTORS									
Hospital admission (%)	81.3	78.7	0.388	95.3	95.6	0.879	93.8	82.4	0.316
Stroke type (%)									
Ischaemic stroke	88.8	86.3	**0.004**	85.2	84.7	0.063	75.0	94.1	0.411
Intracerebral haemorrhage	5.7	5.2		12.7	8.7		6.3	0.0	
Subarachnoid haemorrhage	1.3	6.1		0.0	0.4		12.5	5.9	
Undetermined	4.2	2.4		2.2	6.1		6.3	0.0	
Time to arrive hospital (%)*									
≤ 4.5 hours	-	-	-	27.1	22.8	0.596	13.3	21.4	0.396
> 4.5 – 24 hours				12.9	12.8		6.7	14.3	
> 24 hours				8.9	7.3		6.7	21.4	

Supplemental Table C-1. Baseline characteristics by sex and outcomes of survivors at 1 year after stroke with HRQoL assessment among studies conducted in Oxford, Melbourne and Perth

Characteristic	Oxford			Melbourne			Perth		
	Men (n=384)	Women (n=328)	p-value	Men (n=236)	Women (n=229)	p-value	Men (n=16)	Women (n=17)	p-value
Unknown				51.1	57.1		73.3	42.9	
Stroke severity									
NIHSS, mean (SD)	3.2 (8.4)	3.4 (4.5)	0.385	4.7 (4.8)	5.4 (5.4)	0.168	5.0 (5.7)	5.3 (7.1)	0.916
TREATMENT AND MANAGEMENT*									
Admission medication (%)									
Antihypertensives	-	-	-	52.4	57.1	0.327	33.3	57.1	0.198
Antiplatelet	-	-	-	34.5	33.5	0.831	20.0	35.7	0.427
Anticoagulant	-	-	-	4.6	4.7	0.973	13.3	0.0	0.483
Discharge medication (%)									
Antihypertensives	-	-	-	47.1	51.1	0.713	53.3	64.3	0.550
Antiplatelet†	-	-	-	56.7	59.7	0.553	45.5	76.9	0.113
Anticoagulant†	-	-	-	21.1	15.2	0.130	45.5	0.0	**0.011**
Investigation (%)									
Neuroimaging	-	-	-	97.3	95.0	0.196	53.3	64.3	0.550
Carotid investigation†	-	-	-	59.7	59.8	0.984	27.3	0.0	0.082
Echocardiography†	-	-	-	51.5	37.2	**0.009**	36.4	7.7	0.112
POST-STROKE FACTORS									
Mood disorder									
Depression (IDA subscale ≥ 8)									
Yes	-	-	-	16.1	17.5	0.178	-	-	-
No				72.0	65.1				
Unknown				11.9	17.5				
IDA subscale – Depression, median (IQR)	-	-	-	3.0 (1.0-5.5)	4.0 (2.0-6.0)	**0.017**	-	-	-
IDA subscale – Anxiety, median (IQR)	-	-	-	2.5 (0.0-5.0)	4.0 (1.0-7.0)	**0.001**	-	-	-
IDA total score, median (IQR)	-	-	-	8.0 (4.0-12.0)	11.0 (7.0-16.0)	0.059	-	-	-
Stroke recurrence ≤ 1 year (%)	-	-	-	0.9	0.4	0.580			
Modified Rankin Score (%)									
0-2	23.4	34.5	**0.001**	-	-	-	76.2	76.2	**0.001**
3-5	76.6	65.6					23.8	23.8	
Unknown	0.0	0.0					0.0	0.0	
Barthel Index Score (%)									
20	-	-	-	61.0	43.7	**0.001**	-	-	-
<20				37.7	54.6				
Unknown				1.3	1.8				
OUTCOME AT 1 YEAR									
EQ5D utility, mean (SD)	0.75 (0.28)	0.67 (0.90)	**<0.001**	-	-	-	-	-	-
EQ5D utility, median (IQR)	0.80 (0.66-1.00)	0.73 (0.62-0.85)	**<0.001**	-	-	-	-	-	-
AQoL utility, mean (SD)	-	-	-	0.57 (0.33)	0.45 (0.32)	**<0.001**	-	-	-

Supplemental Table C-1. Baseline characteristics by sex and outcomes of survivors at 1 year after stroke with HRQoL assessment among studies conducted in Oxford, Melbourne and Perth

Characteristic	Oxford			Melbourne			Perth		
	Men (n=384)	Women (n=328)	p-value	Men (n=236)	Women (n=229)	p-value	Men (n=16)	Women (n=17)	p-value
AQoL utility, median (IQR)	-	-	-	0.64 (0.28-0.88)	0.45 (0.13-0.72)	**<0.01**	-	-	-
SF6D, mean (SD)	-	-	-	-	-	-	0.75 (0.12)	0.57 (0.11)	**<0.01**
SF6D, median (IQR)	-	-	-	-	-	-	0.78 (0.63-0.81)	0.57 (0.51-0.63)	**<0.01**

AQoL=Assessment of Quality of Life; EQ5D=European Quality of Life–5 Dimensions; SF36=Short form–36 questions

*among hospitalised patients; †among those with ischaemic strokes

Supplemental Table C-2. Baseline characteristic of survivors at 5 years after stroke with HRQoL assessment among studies conducted in Oxford, Melbourne and Auckland

Characteristic	Oxford			Melbourne			Auckland		
	Men (n=139)	Women (n=130)	p-value	Men (n=236)	Women (n=229)	p-value	Men (n=183)	Women (n=155)	p-value
SOCIODEMOGRAPHIC									
Age, mean (SD)	67.9 (9.6)	69.7 (12.0)	0.170	68.1 (13.4)	70.1 (15.3)	0.132	64.1 (4.1)	75.5 (2.5)	**0.024**
Race (%)									
Caucasian	-	-	-	90.8	96.4	**0.014**	-	-	-
Non-Caucasian				3.5	2.7				
Unknown				5.7	0.9				
Marital status (%)									
Single/widowed	18.0	43.9	**<0.001**	-	-	-	26.2	47.7	**<0.001**
Married	74.0	49.2					73.8	52.3	
Unknown	8.6	6.9					0.0	0.0	
Education level (%)									
≤ Grade 12	79.1	82.3	0.428	37.4	35.9	**0.010**	37.2	59.4	**<0.001**
> Grade 12	16.6	13.1		54.2	61.9		53.6	35.5	
Unknown	4.3	4.6		8.4	2.2		9.3	5.2	
Social class (%)									
Professional	13.7	4.6	**0.004**	37.9	35.9	0.232	27.9	18.1	**<0.001**
Non-manual	20.9	37.7		11.0	12.1		15.3	30.3	
Manual	50.4	43.1		41.9	36.8		49.2	21.9	
Unknown	15.1	14.6		9.3	15.3		7.7	29.7	
PRE-STROKE HEALTH									
Institutional residence (%)									
Yes	-	-	-	2.2	7.2	**0.038**	-	-	-
No				96.9	91.5				
Unknown				0.9	1.4				
Modified Rankin Score (%)									
0-2	98.6	94.6	0.072	-	-	-	-	-	-
3-5	1.4	5.4							
Unknown	0.0	0.0							
Barthel Index score (%)									
20	-	-	-	6.6	13.5	**0.040**	-	-	-
<20				73.6	65.5				
Unknown				19.8	21.1				
Pre-stroke dependence (%)									
Yes	-	-	-	-	-	-	3.3	8.4	0.085
No							96.2	91.6	
Unknown							0.6	0.0	
MEDICAL HISTORY									
Hypertension (%)									
Yes	55.4	63.9	0.158	51.1	57.9	0.152	54.1	56.8	0.874
No	44.6	36.2		48.0	42.2		45.4	42.6	
Unknown	0.3	0.0		0.9	0.0		0.6	0.7	
Atrial fibrillation (%)									
Yes	11.5	9.2	0.541	11.9	14.8	0.255	12.0	19.4	0.063
No	88.5	90.8		87.2	85.2		88.0	80.7	
Unknown	0.0	0.0		0.9	0.0		0.0	0.0	
Ischaemic heart disease (%)									
Yes	13.7	5.4	**0.043**	13.2	9.0	0.127	20.2	12.3	0.050
No	85.6	94.6		85.9	91.0		79.8	87.7	
Unknown	0.7	0.0		0.9	0.0		0.0	0.0	
Peripheral vascular disease (%)									
Yes	6.5	3.9	0.332	7.1	3.6	0.220	-	-	-
No	93.5	96.2		92.1	96.0				
Unknown	0.0	0.0		0.9	0.5				
Transient ischaemic attack (%)									
Yes	11.5	11.5	0.994	8.4	9.0	0.975	-	-	-
No	88.5	88.5		91.2	90.6				
Unknown	0.0	0.0		0.4	0.5				
Diabetes (%)									
Yes	13.0	7.7	0.158	20.7	15.3	0.112	-	-	-

Supplemental Table C-2. Baseline characteristic of survivors at 5 years after stroke with HRQoL assessment among studies conducted in Oxford, Melbourne and Auckland

Characteristic	Oxford			Melbourne			Auckland		
	Men (n=139)	Women (n=130)	p-value	Men (n=236)	Women (n=229)	p-value	Men (n=183)	Women (n=155)	p-value
No	87.1	92.3		78.4	84.8				
Unknown	0.0	0.0		0.9	0.0				
Dementia (%)									
Yes	-	-	-	0.0	3.6	**0.004**	0.6	0.0	**0.357**
No				79.3	76.2		99.5	100.0	
Unknown				20.7	20.2		0.0	0.0	
Smoking (%)									
Current	51.1	26.9	**<0.001**	48.0	20.2	**<0.001**	57.9	51.6	**<0.001**
Former	21.6	18.5		16.7	14.4		12.0	37.4	
Never	27.3	53.9		31.2	60.1		29.5	10.3	
Unknown	0.0	0.8		4.0	5.4		0.6	0.7	
Alcohol use (%)									
Non-drinkers	23.7	50.8	**<0.001**	17.6	47.5	**<0.001**	16.4	40.7	**<0.001**
Not heavy drinkers	71.2	41.5		62.1	43.1		71.6	41.9	
Heavy drinkers	4.3	4.6		9.3	1.8		10.4	16.1	
Ex-drinkers	-	-		6.6	0.5		1.6	1.3	
Unknown	0.7	3.1		4.4	7.2		12.5	11.8	
Pre-stroke medication									
Antihypertensives (%)									
Yes	-	-	-	47.6	53.4	0.369	42.1	42.6	0.527
No				52.0	45.7		4.4	7.1	
Unknown				0.4	0.9		53.6	50.3	
Antiplatelet (%)									
Yes	-	-	-	29.1	28.7	0.996	32.2	27.7	0.667
No				70.5	70.9		67.2	71.6	
Unknown				0.4	0.5		0.6	0.7	
STROKE-RELATED FACTORS									
Hospital admission (%)	59.7	60.0	0.962	92.5	94.6	0.363	97.3	95.5	0.378
Stroke type (%)									
Ischaemic stroke	92.8	83.1	**0.030**	83.3	85.7	0.496	84.2	76.1	0.324
Intracerebral haemorrhage	3.6	4.6		14.1	10.8		91.8	11.6	
Subarachnoid haemorrhage	1.4	9.2		0.0	0.0		4.9	7.7	
Undetermined	2.2	3.1		2.6	3.6		3.3	4.5	
Time to arrive hospital* (%)									
≤ 4.5 hours	-	-	-	23.8	25.1	0.182	79.2	81.1	0.801
> 4.5 – 24 hours				14.8	8.1		15.2	14.9	
> 24 hours				8.1	10.0		5.6	4.1	
Unknown				53.3	56.9		73.3	42.9	
Stroke severity									
NIHSS, mean (SD)	3.2 (8.4)	3.4 (4.5)	0.385	4.3 (4.5)	5.2 (5.4)	0.090	-	-	-
Reversed GCS, mean (SD)	-	-	-	-	-	-	1.6 (1.7)	1.7 (2.0)	0.573
TREATMENT AND MANAGEMENT*									
Admission medication (%)									
Antihypertensives	-	-	-	47.6	53.4	0.220	-	-	-
Antiplatelet	-	-	-	32.3	28.8	0.461	-	-	-
Anticoagulant	-	-	-	3.7	6.3	0.249	-	-	-
Discharge medication (%)									
Antihypertensives	-	-	-	46.3	47.5	0.786	66.3	65.3	0.852
Antiplatelet†	-	-	-	59.3	59.2	0.985	86.8	85.1	0.698
Anticoagulant†	-	-	-	19.6	18.9	0.857	17.2	16.7	0.906
Investigation (%)									
Neuroimaging	-	-	-	96.2	96.7	0.785	92.7	91.9	0.786
Carotid investigation†	-	-	-	62.2	62.3	0.985	8.6	5.3	0.296
Echocardiography†	-	-	-	52.0	41.5	0.065	2.0	0.0	0.130
POST-STROKE FACTORS									
Modified Rankin Score (%)									

Supplemental Table C-2. Baseline characteristic of survivors at 5 years after stroke with HRQoL assessment among studies conducted in Oxford, Melbourne and Auckland

Characteristic	Oxford			Melbourne			Auckland		
	Men (n=139)	Women (n=130)	p-value	Men (n=236)	Women (n=229)	p-value	Men (n=183)	Women (n=155)	p-value
0-2	20.1	36.9	**0.002**	-	-	-	71.0	75.5	0.387
3-5	79.9	63.1					24.6	22.6	
Unknown	0.0	0.0					4.4	1.9	
Barthel Index Score (%)									
20	-	-	-	43.2	53.8	**0.042**	-	-	-
<20				56.8	45.7				
Unknown				0.0	0.5				
Mood disorder									
Depression (IDA score ≥7 or PHQ score ≥8)									
Yes	-	-	-	11.9	14.4	0.681	31.2	29.7	0.957
No				76.8	74.9		47.5	48.4	
Unknown				12.3	10.8		21.3	21.9	
IDA subscale - depression, median (IQR)	-	-	-	3.0 (1.0-5.0)	3.0 (1.0-6.0)	0.505	-	-	-
IDA subscale - anxiety, median (IQR)	-	-	-	2.0 (0.0-4.0)	3.0 (0.0-5.0)	**0.029**	-	-	-
IDA total score, median (IQR)	-	-	-	9.0 (5.0-13.0)	10.0 (7.0-15.0)	0.337	-	-	-
PHQ anxiety, median (IQR)	-	-	-	-	-	-	2.0 (0.0-4.0)	2.0 (0.0-5.0)	0.164
PHQ depression, median (IQR)	-	-	-	-	-	-	0.0 (0.0-1.0)	0.0 (0.0-3.0)	0.890
Use of antidepressant medications at 5 years (%)									
Yes	-	-	-	15.4	24.7	**0.047**	-	-	-
No				73.1	65.9				
Unknown				11.5	9.4				
Use of antidepressant medications among those with depression (5-year IDA ≥7; %)	-	-	-	18.5	21.9	0.175	-	-	-
Use of antidepressant medications among those without depression (5-year IDA <7; %)				16.3	27.0	**0.017**			
Of those with antidepressant medications, % reported no depression (5-year IDA <7)				84.9	86.5	0.827			
Stroke recurrence ≤ 5 years (%)	-	-	-	8.8	9.0	0.953	15.3	18.1	0.496
OUTCOME AT 5 YEARS									
EQ5D utility, mean (SD)	0.76 (0.26)	0.66 (0.31)	**0.007**	-	-	-	-	-	-
EQ5D utility, median (IQR)	0.80 (0.69-1.00)	0.71 (0.59-0.85)	**0.003**	-	-	-	-	-	-
AQoL utility, mean (SD)	-	-	-	0.55 (0.35)	0.43 (0.33)	**<0.001**	-	-	-
AQoL utility, median (IQR)	-	-	-	0.64 (0.19-0.87)	0.45 (0.08-0.71)	**<0.001**	-	-	-
SF6D, mean (SD)	-	-	-	-	-	-	0.77 (0.13)	0.72 (0.13)	**<0.001**
SF6D, median (IQR)	-	-	-	-	-	-	0.79 (0.68-0.85)	0.72 (0.61-0.85)	**<0.001**

*among hospitalised patients; †among those with ischaemic strokes

Supplemental Table C-3. Characteristics of people with and without 1-year health-related quality of life assessment after stroke

	Oxford				Melbourne				Perth			
	Assessed		Unassessed		Assessed		Unassessed		Assessed		Unassessed	
Characteristic	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Number of cases	384 (54%)	328 (46%)	138 (50%)	138 (50%)	236 (51%)	229 (49%)	172 (45%)	208 (55%)	16 (52%)	17 (48%)	39 (45%)	48 (55%)
SOCIODEMOGRAPHIC												
Mean (SD) Age	**70.1 (12.2)**	**72.7 (12.7)**	**69.5 (13.6)**	**76.5 (13.6)**	**70.6 (12.5)**	**73.4 (14.4)**	**68.5 (15.4)**	**71.6 (17.0)**	64.1 (16.5)	75.5 (10.5)	**74.6 (12.1)**	**77.5 (12.4)**
Marital status (%)												
Single/widowed	**20.3**	**48.5**	**26.8**	**46.4**	-	-	-	-	37.5	52.9	-	-
Married	**74.2**	**47.9**	**50.7**	**31.9**					62.5	47.1		
Unknown	**5.5**	**3.7**	**22.5**	**21.7**					0.0	0.0		
Education level (%)												
≤ Grade 12	73.2	80.2	53.6	50.7	**66.1**	**78.2**	**29.7**	**67.3**	-	-	-	-
> Grade 12	19.3	14.3	10.1	4.4	**25.9**	**19.7**	**66.9**	**32.7**				
Unknown	7.6	5.5	36.2	44.9	**8.1**	**2.2**	**3.5**	**0.0**				
Social class (%)												
Professional	**20.1**	**8.2**	**10.9**	**4.4**	35.2	34.5	**39.5**	**27.9**	25.0	17.7	**15.5**	**3.8**
Non-manual	**23.7**	**39.6**	**14.5**	**23.9**	14.0	14.4	**5.8**	**11.5**	12.5	23.5	**5.6**	**6.3**
Manual	**45.6**	**39.6**	**10.6**	**27.5**	47.9	47.6	**36.6**	**22.6**	56.3	41.2	**28.2**	**16.5**
Unknown	**10.7**	**12.5**	**34.1**	**44.2**	3.0	3.5	**18.0**	**38.0**	6.3	17.7	**50.7**	**73.4**
PRE-STROKE HEALTH												
In an institution (%)												
Yes	-	-	-	-	4.3	7.4	**4.7**	**13.0**	0.0	21.4	9.9	17.7
No					95.8	92.1	**91.9**	**85.1**	100.0	78.6	87.3	78.5
Unknown					0.0	0.4	**3.5**	**1.9**	0.0	0.0	1.8	3.8
Modified Rankin Score (%)												
0-2	**93.8**	**86.6**	79.7	73.9	-	-	-	-	**93.8**	**58.8**	66.2	24.1
3-5	**6.0**	**13.1**	14.5	22.5					**6.3**	**41.2**	22.5	55.7
Unknown	**0.3**	**0.3**	5.8	3.6					**0.0**	**0.0**	11.3	20.3
Barthel Index score (%)												
20	-	-	-	-	**84.3**	**75.1**	33.7	26.4	-	-	-	-
<20					**12.7**	**20.1**	5.2	9.6				
Unknown					**3.0**	**4.8**	61.1	63.9				
MEDICAL HISTORY												
Hypertension (%)												
Yes	58.9	62.8	60.9	57.3	51.3	58.1	49.4	57.2	37.5	58.8	66.7	58.3
No	40.9	37.2	39.1	42.8	48.7	41.9	48.8	42.3	62.5	41.2	28.2	37.5
Unknown	0.3	0.0	0.0	0.0	0.0	0.0	1.7	0.5	0.0	0.0	5.1	4.2
Atrial fibrillation (%)												
Yes	15.4	15.6	17.4	18.8	16.5	16.2	14.0	21.6	12.5	17.7	20.6	22.9
No	84.6	84.5	82.6	81.2	82.2	83.8	84.9	77.4	87.5	82.4	71.8	68.8
Unknown	0.0	0.0	0.0	0.0	1.3	0.0	1.2	1.0	0.0	0.0	7.7	8.3
Ischaemic heart disease (%)												
Yes	**14.6**	**7.9**	14.8	8.0	16.1	10.0	12.2	9.1	25.0	5.9	12.8	4.2
No	**85.2**	**92.1**	85.5	92.0	83.9	90.0	86.6	89.9	75.0	94.1	82.1	89.6
Unknown	**0.3**	**0.0**	0.0	0.0	0.0	0.0	1.2	1.0	0.0	0.0	5.1	6.3
Peripheral vascular disease (%)												
Yes	5.7	3.7	9.4	5.1	**10.2**	**4.8**	9.9	3.9	-	-	-	-
No	93.8	96.3	90.6	93.5	**89.8**	**95.2**	89.0	95.2				
Unknown	0.5	0.0	0.0	1.5	**0.0**	**0.0**	1.2	1.0				
Transient ischaemic attack (%)												
Yes	13.8	12.2	10.9	10.0	9.8	10.9	7.0	5.8	31.3	11.8	18.0	6.3
No	86.2	87.8	89.1	89.1	89.8	89.1	92.4	93.8	62.5	88.2	69.2	85.4
Unknown	0.0	0.0	0.0	0.7	0.4	0.0	0.6	0.5	6.3	0.0	12.8	8.3
Diabetes (%)												
Yes	14.1	10.7	18.8	11.6	19.1	16.2	**22.1**	**12.0**	18.8	23.5	15.4	16.7
No	85.9	89.3	80.4	88.4	80.5	83.8	**77.3**	**88.0**	81.3	76.5	82.1	83.3
Unknown	0.0	0.0	0.7	0.0	0.4	0.0	**0.6**	**0.0**	0.0	0.0	2.6	0.0
Dementia (%)												
Yes	-	-	-	-	**2.1**	**5.7**	**2.3**	**8.2**	-	-	-	-
No					**76.3**	**72.1**	**76.2**	**76.0**				
Unknown					**21.6**	**22.3**	**21.5**	**15.9**				
Smoking (%)												

Supplemental Table C-3. Characteristics of people with and without 1-year health-related quality of life assessment after stroke

	Oxford				Melbourne				Perth			
	Assessed		Unassessed		Assessed		Unassessed		Assessed		Unassessed	
Characteristic	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Current	**51.8**	**26.8**	**46.4**	**29.0**	**51.3**	**21.4**	**39.0**	**20.2**	**68.8**	**52.9**	**48.7**	**10.4**
Former	**18.2**	**17.4**	**21.7**	**13.8**	**14.8**	**14.0**	**26.2**	**14.4**	**18.8**	**5.9**	**10.3**	**6.3**
Never	**29.7**	**55.2**	**29.0**	**50.7**	**33.1**	**62.9**	**22.1**	**47.6**	**0.0**	**35.3**	**25.6**	**56.3**
Unknown	**0.3**	**0.6**	**2.9**	**6.5**	**0.9**	**1.8**	**12.8**	**17.8**	**12.5**	**5.9**	**15.4**	**27.1**
Alcohol use (%)												
Non-drinkers	**23.7**	**53.7**	**34.1**	**57.3**	**19.9**	**44.5**	**19.8**	**41.4**	18.8	29.4	30.8	25.0
Not heavy drinkers	**71.1**	**42.4**	**49.3**	**24.6**	**65.3**	**50.2**	**44.8**	**35.1**	0.0	23.5	10.3	14.6
Heavy drinkers	**3.7**	**2.1**	**2.9**	**2.2**	**7.2**	**1.3**	**11.1**	**1.4**	56.3	35.3	25.6	14.6
Ex-drinkers	**-**	**-**	**-**	**-**	**5.9**	**0.4**	**8.1**	**1.0**	12.5	0.0	5.1	6.3
Unknown	**1.6**	**1.8**	**13.8**	**15.9**	**1.7**	**3.5**	**16.3**	**21.2**	12.5	11.8	28.2	39.6
STROKE-RELATED FACTORS												
Hospital admission (%)	81.3	78.7	84.1	89.9	95.3	95.6	94.2	93.8	93.8	82.4	84.6	83.3
Stroke type (%)												
Ischaemic stroke	**88.8**	**86.3**	83.3	75.4	85.2	84.7	72.7	72.1	75.0	94.1	89.7	75.0
Intracerebral haemorrhage	**5.7**	**5.2**	4.4	8.7	12.7	8.7	15.7	9.1	6.3	0.0	7.7	8.3
Subarachnoid haemorrhage	**1.3**	**6.1**	1.5	5.8	0.0	0.4	6.4	13.5	12.5	5.9	2.6	8.3
Undetermined	**4.2**	**2.4**	10.9	10.1	2.2	6.1	5.2	5.3	6.3	0.0	0.0	8.3
Stroke severity												
Mean (SD) NIHSS	3.2 (8.4)	3.4 (4.5)	4.8 (5.7)	5.5 (6.6)	4.7 (4.8)	5.4 (5.4)	5.6 (6.2)	6.3 (7.6)	5.0 (5.7)	5.3 (7.1)	7.2 (7.0)	8.3 (7.3)

Supplemental Table C-4. Characteristics of people with and without 5-year health-related quality of life assessment after stroke

	Oxford				Melbourne				Auckland			
	Assessed		Unassessed		Assessed		Unassessed		Assessed		Unassessed	
Characteristic	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Number of cases	139 (%)	130 (%)	227 (%)	223 (%)	236 (51%)	229 (49%)	172 (45%)	208 (55%)	188 (%)	155 (%)	71 (%)	79 (%)
SOCIODEMOGRAPHIC												
Mean (SD) Age	67.9 (9.6)	69.7 (12.0)	68.1 (13.4)	70.1 (15.3)	68.1 (13.4)	70.1 (15.3)	61.3 (15.6)	62.2 (18.1)	**64.5 (12.5)**	**68.3 (12.5)**	**70.3 (13.8)**	**76.2 (14.2)**
Marital status (%)												
Single/widowed	**18.0**	**43.9**	**29.0**	**55.6**	-	-	-	-	**26.2**	**47.7**	**34.9**	**65.7**
Married	**74.0**	**49.2**	**56.5**	**36.1**					**73.8**	**52.3**	**62.0**	**29.5**
Unknown	**8.6**	**6.9**	**14.5**	**8.3**					**0.0**	**0.0**	**3.1**	**4.8**
Education level (%)												
≤ Grade 12	79.1	82.3	**61.3**	**63.9**	**37.4**	**35.9**	11.5	45.4	**37.2**	**59.4**	**38.8**	**46.8**
> Grade 12	16.6	13.1	**4.8**	**9.7**	**54.2**	**61.9**	49.9	53.6	**53.6**	**35.5**	**29.8**	**19.8**
Unknown	4.3	4.6	**33.9**	**26.4**	**8.4**	**2.2**	5.6	1.1	**9.3**	**5.2**	**31.4**	**33.4**
Social class (%)												
Professional	**13.7**	**4.6**	11.3	8.3	37.9	35.9	37.5	30.6	**27.9**	**18.1**	**21.3**	**9.8**
Non-manual	**20.9**	**37.7**	9.7	12.5	11.0	12.1	10.8	12.3	**15.3**	**30.3**	**15.7**	**20.3**
Manual	**50.4**	**43.1**	50.0	47.2	41.9	36.8	43.3	32.4	**49.2**	**21.9**	**37.6**	**16.6**
Unknown	**15.1**	**14.6**	29.0	31.9	9.3	15.3	8.3	24.7	**7.7**	**29.7**	**25.4**	**53.2**
PRE-STROKE HEALTH												
Pre-stroke dependence (%)												
Yes	-	-	-	-	-	-	-	-	3.3	8.4	11.0	25.5
No									96.2	91.6	84.3	69.4
Unknown									0.6	0.0	4.8	5.0
Modified Rankin Score (%)												
0-2	98.6	94.6	87.1	79.2	-	-	-	-	-	-	-	-
3-5	1.4	5.4	9.7	20.8								
Unknown	0.0	0.0	3.2	0.0								
Barthel Index score (%)												
20	-	-	-	-	**6.6**	**13.5**	42.7	33.8	-	-	-	-
<20					**73.6**	**65.5**	5.9	6.8				
Unknown					**19.8**	**21.1**	51.5	59.5				
MEDICAL HISTORY												
Hypertension (%)												
Yes	55.4	63.9	58.1	54.2	51.1	57.9	50.0	46.0	54.1	56.8	**48.6**	**56.9**
No	44.6	36.2	41.9	45.8	48.0	42.2	50.0	52.7	45.4	42.6	**45.7**	**38.1**
Unknown	0.3	0.0	0.0	0.0	0.9	0.0	0.0	1.4	0.6	0.7	**5.8**	**5.0**
Atrial fibrillation (%)												
Yes	11.5	9.2	19.4	18.1	11.9	14.8	14.7	10.8	12.0	19.4	19.6	24.1
No	88.5	90.8	80.7	81.9	87.2	85.2	85.3	87.8	88.0	80.7	77.5	72.9
Unknown	0.0	0.0	0.0	0.0	0.9	0.0	0.0	1.4	0.0	0.0	2.9	3.0
Ischaemic heart disease (%)												
Yes	13.7	5.4	11.3	6.9	13.2	9.0	**10.3**	**1.4**	20.2	12.3	24.6	19.6
No	85.6	94.6	88.7	93.1	85.9	91.0	**89.7**	**97.3**	79.8	87.7	74.0	78.6
Unknown	0.7	0.0	0.0	0.0	0.9	0.0	**0.0**	**1.4**	0.0	0.0	1.5	1.8
Peripheral vascular disease (%)												
Yes	6.5	3.9	9.7	5.6	7.1	3.6	7.4	4.1	-	-	-	-
No	93.5	96.2	90.3	94.4	92.1	96.0	82.7	94.6				
Unknown	0.0	0.0	0.0	0.0	0.9	0.5	0.0	1.4				
Transient ischaemic attack (%)												
Yes	11.5	11.5	17.7	25.0	8.4	9.0	4.4	8.1	-	-	-	-
No	88.5	88.5	82.3	75.0	91.2	90.6	84.1	91.9				
Unknown	0.0	0.0	0.0	0.0	0.4	0.5	1.5	0.0				
Diabetes (%)	13.0	7.7	9.7	5.6	20.7	15.3	17.7	8.1				
Yes	87.1	92.3	88.7	94.4	78.4	84.8	82.4	81.9	-	-	-	-
No	0.0	0.0	1.6	0.0	0.9	0.0	0.0	0.0				
Unknown												
Smoking (%)												
Current	51.1	26.9	**50.0**	**23.6**	**48.0**	**20.2**	**36.8**	**13.5**	**57.9**	**51.6**	**46.9**	**27.1**
Former	21.6	18.5	**22.6**	**23.6**	**16.7**	**14.4**	**25.3**	**21.6**	**12.0**	**37.4**	**17.8**	**45.8**
Never	27.3	53.9	**25.8**	**52.8**	**31.2**	**60.1**	**17.7**	**52.7**	**29.5**	**10.3**	**25.6**	**45.8**

Supplemental Table C-4. Characteristics of people with and without 5-year health-related quality of life assessment after stroke

	Oxford				Melbourne				Auckland			
	Assessed		Unassessed		Assessed		Unassessed		Assessed		Unassessed	
Characteristic	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Unknown	0.0	0.8	**1.6**	**0.0**	**4.0**	**5.4**	**10.3**	**12.2**	**0.6**	**0.7**	**9.7**	**15.0**
Alcohol use (%)												
Non-drinkers	23.7	50.8	**25.8**	**55.6**	**17.6**	**47.5**	**23.5**	**37.8**	**16.4**	**40.7**	**21.7**	**43.3**
Not heavy drinkers	71.2	41.5	**62.9**	**36.1**	**62.1**	**43.1**	**47.1**	**10.5**	**71.6**	**41.9**	**47.1**	**27.0**
Heavy drinkers	4.3	4.6	**3.2**	**4.2**	**9.3**	**1.8**	**8.8**	**1.4**	**10.4**	**16.1**	**15.3**	**11.3**
Ex-drinkers	**-**	**-**	**-**	**-**	**6.6**	**0.5**	**5.9**	**0.0**	**1.6**	**1.3**	**15.9**	**18.3**
Unknown	0.7	3.1	**8.1**	**4.2**	**4.4**	**7.2**	**14.7**	**20.3**	**0.0**	**0.0**	**0.0**	**0.0**
STROKE-RELATED FACTORS												
Hospital admission (%)	59.7	60.0	75.8	76.4	92.5	94.6	95.6	97.3	97.3	95.5	**94.6**	**89.2**
Stroke type (%)												
Ischaemic stroke	**92.8**	**83.1**	88.7	77.8	83.3	85.7	**69.1**	**51.4**	84.2	76.1	**73.1**	**67.6**
Intracerebral haemorrhage	**3.6**	**4.6**	6.5	6.9	14.1	10.8	**11.8**	**8.1**	91.8	11.6	**13.6**	**13.1**
Subarachnoid haemorrhage	**1.4**	**9.2**	1.6	9.7	0.0	0.0	**16.2**	**37.8**	4.9	7.7	**6.6**	**5.7**
Undetermined	**2.2**	**3.1**	3.2	5.6	2.6	3.6	**2.9**	**2.7**	3.3	4.5	**6.6**	**13.6**
Stroke severity												
Mean (SD) NIHSS	2.8 (3.4)	2.9 (4.3)	3.9 (4.4)	4.5 (6.0)	4.3 (4.5)	5.2 (5.4)	4.0 (4.3)	5.4 (7.7)	**-**	**-**	**-**	**-**
Mean (SD) GCS, reversed	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1.6 (1.7)**	**1.7 (2.0)**	**2.9 (3.4)**	**3.4 (3.6)**

Supplemental Table C-5. Comparison of complete-case and imputed analyses of median difference (MD) in utility scores between women and men

Study	Unadjusted			Adjusted		
	Complete-case	**IPW**	**Imputation & IPW**	**Complete-case**	**IPW**	**Imputation & IPW**
	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)
Oxford						
1-year	**-0.069 (-0.089, -0.049)**	**-0.069 (-0.105, -0.032)**	**-0.086 (-0.123, -0.049)**	**-0.049 (-0.094, -0.003)**	**-0.042 (-0.080, -0.004)**	**-0.048 (-0.092, -0.005)**
5-year	**-0.086 (0.122, -0.050)**	**-0.086 (-0.135, -0.037)**	**-0.093 (-0.158, -0.028)**	-0.071 (-0.142, 0.000)	-0.063 (-0.116, -0.010)	-0.056 (-0.134, 0.021)
Melbourne						
1-year	**-0.197 (-0.334, -0.060)**	**-0.210 (-0.305, -0.115)**	**-0.188 (-0.290, -0.086)**	**-0.076 (-0.145, -0.007)**	**-0.096 (-0.149, -0.044)**	**-0.069 (-0.128, -0.010)**
5-year	**-0.165 (-0.306, -0.024)**	**-0.228 (-0.327, -0.129)**	**-0.158 (-0.281, -0.035)**	**-0.153 (-0.241, -0.064)**	**-0.146 (-0.212, -0.080)**	**-0.128 (-0.223, -0.033)**
Perth						
1-year	**-0.210 (-0.308, -0.112)**	**-0.216 (-0.273, -0.159)**	**-0.163 (-0.302, -0.023)**	**-0.187 (-0.340, -0.015)**	**-0.182 (-0.268, -0.096)**	-0.135 (-0.285, 0.016)
Auckland						
5-year	**-0.090 (-0.119, -0.062)**	**-0.091 (-0.124, -0.058)**	**-0.067 (-0.111, -0.025)**	**-0.059 (-0.110, -0.008)**	**-0.045 (-0.069, -0.020)**	**-0.049 (-0.092, -0.006)**

IPW=Inverse probability weighting

Supplemental Table C-6. Median differences (MD) in AQoL domains in the Melbourne study

	Unadjusted		Adjusted*		
	MD	95% CI	MD	95% CI	Covariates†
1 year					
Illness	-0.05	-0.13, 0.03	-0.02	-0.09, 0.05	Age
Independent living	**-0.23**	**-0.37, -0.10**	**-0.09**	**-0.14, -0.04**	Age, severity, pre-stroke Barthel
Social relationships	-0.04	-0.10, 0.02	-0.02	-0.05, 0.002	Severity, pre-stroke Barthel, 1-year depression
Physical senses	0	-0.08, 0.08	-0.008	-0.04, 0.02	Age, severity
Psychological well-being	**-0.04**	**-0.05, -0.02**	**-0.03**	**-0.06, -0.004**	Age
5 year					
Illness	0.005	-0.07, 0.08	0.01	-0.06, 0.08	Age
Independent living	**-0.22**	**-0.36, -0.09**	**-0.14**	**-0.24, -0.05**	Age, pre-stroke Barthel
Social relationships	**-0.10**	**-0.19, -0.02**	**-0.04**	**-0.08, -0.01**	Age, severity
Physical senses	0	-0.05, 0.05	0.007	-0.02, 0.04	Age, severity
Psychological well-being	**-0.04**	**-0.06, -0.02**	**-0.06**	**-0.09, -0.03**	5-year depression

*Age, pre-stroke dependency and stroke severity being forced into the final models with covariates meeting our criteria of being confounding factor

† meeting our criteria of being confounding factor

Supplemental Table C-7. Median differences (MD) in SF36 domains in the studies conducted in Perth (1 year) and Auckland (5 years)

	Unadjusted		Adjusted*		
	MD	95% CI	MD	95% CI	Covariates†
Perth (1 year)					
Physical functioning	**-60.0**	**-83.2, -36.8**	**-33.0**	**-64.6, -1.4**	Age
Role physical	-50.0	-107.1, 7.1	-12.6	-80.1, 54.9	No confounders
Bodily pain	-30.8	-78.9, 17.3	-7.2	-60.9, 46.5	Severity
General health	-27.0	-74.2, 12.2	-1.7	-35.4, 32.1	Pre-stroke Rankin
Vitality	**-30.0**	**-53.6, -6.4**	-27.8	-78.7, 23.1	No confounders
Social functioning	-12.5	-41.1, 16.4	-13.9	-66.0, 38.2	No confounders
Role emotional	0	-20.3, 20.3	0	-25.6, 25.6	No confounders
Mental health	-16.0	-34.6, 2.6	-10.6	-35.5, 14.4	No confounders
Overall physical score	**-15.0**	**-22.7, -7.3**	**-11.0**	**-17.9, -4.1**	Age
Overall mental score	-5.7	-16.3, 4.8	-3.8	-21.2, 13.6	No confounders
Auckland (5 years)					
Physical functioning	**-25.0**	**-40.4, -9.6**	-0.77	-11.4, 9.8	Age, pre-stroke dependency
Role physical	-25.0	-66.8, 16.8	-5.0	-66.8, 16.8	No confounders
Bodily pain	-10.0	-30.3, 10.4	-25.0	-20.8, 10.9	No confounders
General health	0	-8.0, 8.0	-5.0	-6.36, 11.9	Pre-stroke dependency
Vitality	-5.0	-15.0, 5.0	2.75	-12.7, 2.8	Age
Social functioning	-12.5	-33.7, 8.7	-12.5	-34.7, 9.7	Pre-stroke dependency
Role emotional	0	-15.8, 18.8	0	-15.8, 18.8	No confounders
Mental health	**-8.0**	**-16.0, -0.006**	**-7.29**	**-12.3, -2.26**	No confounders
Overall physical score	**-4.45**	**-8.63, -0.27**	-0.89	-4.97, 3.20	Age, pre-stroke dependency
Overall mental score	**-2.99**	**-5.17, -0.81**	**-2.99**	**-5.39, -0.58**	Pre-stroke dependency

*Age, pre-stroke dependency and stroke severity, where possible, being forced into the final models with significant confounding factors

† meeting our criteria of being confounding factor

Supplemental Table C-8a. Weighted mean difference in AQoL utility scores between Melbourne survivors at 1 year after stroke and general population

	General population*						Stroke population						Net difference between general and stroke population		
	Male			Female			Male			Female			Male	Female	Female vs Male
Age	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	Mean difference (95% CI)	Mean difference (95% CI)	Net difference
< 55	950	0.85	0.19	645	0.87	0.17	23	0.74	0.31	26	0.69	0.28	0.11 (0.02, 0.24)	0.18 (0.07, 0.29)	0.07
55−64	190	0.82	0.20	188	0.79	0.23	44	0.68	0.33	17	0.55	0.26	0.14 (0.04, 0.24)	0.24 (0.11, 0.37)	0.10
65−74	147	0.80	0.18	154	0.77	0.21	71	0.63	0.30	66	0.54	0.30	0.17 (0.09, 0.25)	0.23 (0.15, 0.31)	0.06
75+	146	0.77	0.24	214	0.70	0.27	98	0.45	0.32	121	0.34	0.30	0.32 (0.25, 0.39)	0.36 (0.30, 0.43)	0.04
Total	1433			1501			236			230					

* Australian norms for AQoL (Hawthorne et al)[276]

Supplemental Table C-8b. Weighted mean difference in AQoL utility scores between Melbourne survivors at 5 years after stroke and general population

	General population*						Stroke population						Net difference between general and stroke population		
	Male			Female			Male			Female			Male	Female	Female vs Male
Age	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	Mean difference (95% CI)	Mean difference (95% CI)	Net difference
< 55	950	0.85	0.19	645	0.87	0.17	30	0.69	0.35	36	0.69	0.25	0.16 (0.03, 0.29)	0.18 (0.10, 0.26)	0.02
55−64	190	0.82	0.20	188	0.79	0.23	48	0.73	0.26	21	0.59	0.31	0.09 (0.01, 0.17)	0.20 (0.06, 0.34)	0.11
65−74	147	0.80	0.18	154	0.77	0.21	75	0.59	0.32	66	0.49	0.30	0.21 (0.13, 0.29)	0.23 (0.15, 0.31)	0.02
75+	146	0.77	0.24	214	0.70	0.27	74	0.35	0.33	100	0.28	0.30	0.42 (0.34, 0.51)	0.42 (0.35, 0.49)	0.00
Total	1433			1501			227			223					

* Australian norms for AQoL (Hawthorne et al)[276]

Supplemental Table C-9a. Weighted mean difference in EQ5D utility scores between Oxford survivors at 1 year after stroke and general population

	General population*						Stroke population						Net difference between general and stroke population		
	Male			Female			Male			Female			Male	Female	Female vs Male
Age	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	Mean difference (95% CI)	Mean difference (95% CI)	Net difference
<55	935	0.90	0.19	1171	0.91	0.17	50	0.71	0.35	41	0.66	0.34	0.19 (0.09, 0.29)	0.25 (0.15, 0.36)	0.06
55−64	196	0.78	0.28	288	0.81	0.26	87	0.66	0.40	54	0.65	0.35	0.12 (0.03, 0.21)	0.16 (0.06, 0.26)	0.04
65−74	228	0.78	0.28	260	0.78	0.25	149	0.67	0.36	105	0.53	0.37	0.11 (0.04, 0.18)	0.25 (0.17, 0.33)	0.14
75+	108	0.75	0.27	206	0.71	0.27	253	0.38	0.41	359	0.28	0.38	0.37 (0.30, 0.44)	0.43 (0.38, 0.48)	0.06
Total	1467			1925			539			559					

*UK norms for EQ5D (Kind et al)[278]

Supplemental Table C-9b. Weighted mean difference in EQ5D utility scores between Oxford survivors at 5 years after stroke and general population

	General population*						Stroke population						Net difference between general and stroke population		
	Male			Female			Male			Female			Male	Female	Female vs Male
Age	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	Mean difference (95% CI)	Mean difference (95% CI)	Net difference
<55	935	0.90	0.19	1171	0.91	0.17	14	0.78	0.29	17	0.79	0.24	0.12 (-0.03, 0.27)	0.12 (0.10, 0.24)	0.00
55−64	196	0.78	0.28	288	0.81	0.26	45	0.79	0.26	28	0.79	0.19	-0.01 (-0.10, 0.08)	0.02 (-0.06, 0.10)	0.03
65−74	228	0.78	0.28	260	0.78	0.25	68	0.77	0.24	43	0.67	0.32	0.01 (-0.06, 0.08)	0.11 (0.01, 0.21)	0.10
75+	108	0.75	0.27	206	0.71	0.27	44	0.70	0.26	53	0.57	0.32	0.05 (-0.04, 0.14)	0.14 (0.05, 0.23)	0.09
Total	1467			1925			171			141					

*UK norms for EQ5D (Kind et al)[278]

Supplemental Table C-10. Weighted mean difference in SF6D utility scores between Auckland survivors at 5 years and general population

	General population*						Stroke population						Net difference between general and stroke population		
	Male			Female			Male			Female			Male	Female	Female vs Male
Age	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	Mean difference (95% CI)	Mean difference (95% CI)	β
< 55	2947	0.78†	0.11	3336	0.77†	0.16	38	0.81	0.12	23	0.74	0.15	-0.03 (-0.07, 0.01)	0.03 (-0.03, 0.09)	0.06
55−64	791	0.76	0.12	915	0.74	0.13	43	0.77	0.14	32	0.72	0.14	-0.01 (-0.05, 0.03)	0.02 (-0.03, 0.07)	0.03
65−74	599	0.75	0.13	654	0.73	0.13	61	0.77	0.11	42	0.74	0.14	-0.02 (-0.05, 0.01)	0.01 (-0.05, 0.03)	0.03
75+	448	0.72	0.13	567	0.69	0.13	41	0.75	0.13	58	0.69	0.12	-0.03 (-0.07, 0.01)	0.00 (-0.03, 0.03)	0.03
Total	5082			5800			183			155					

MD, mean difference;

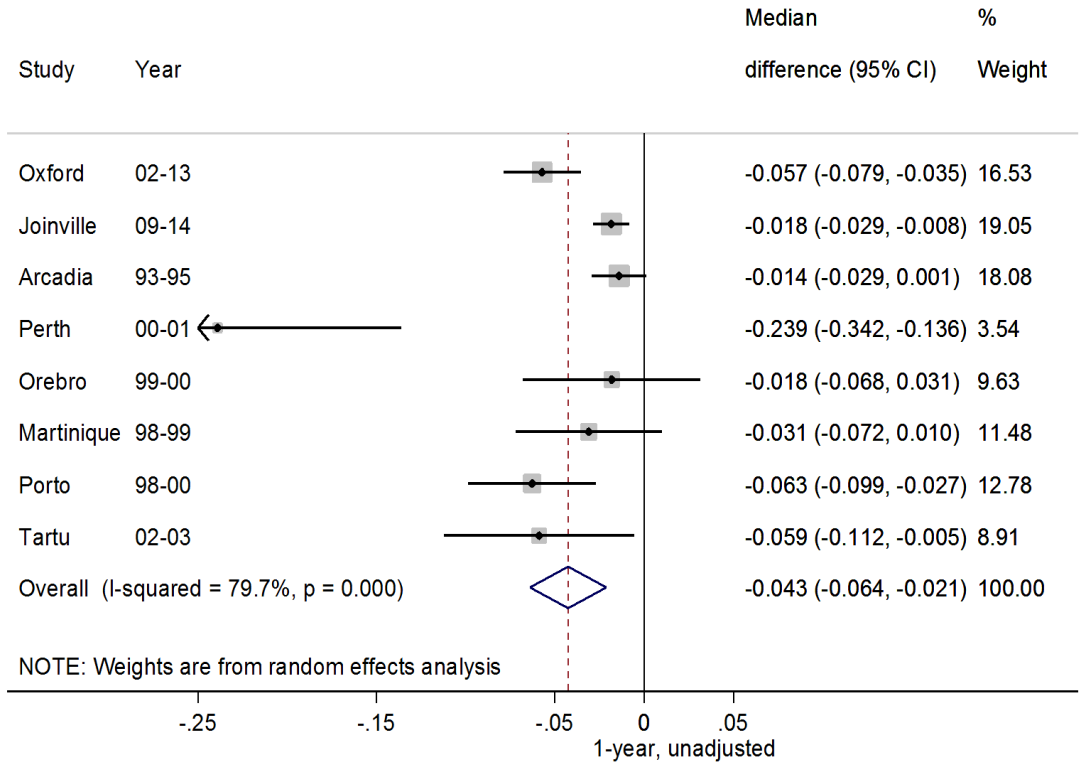
* Australian norms for SF6D (Norman et al)[271] were used because there were no New Zealand reference scores for SF6D

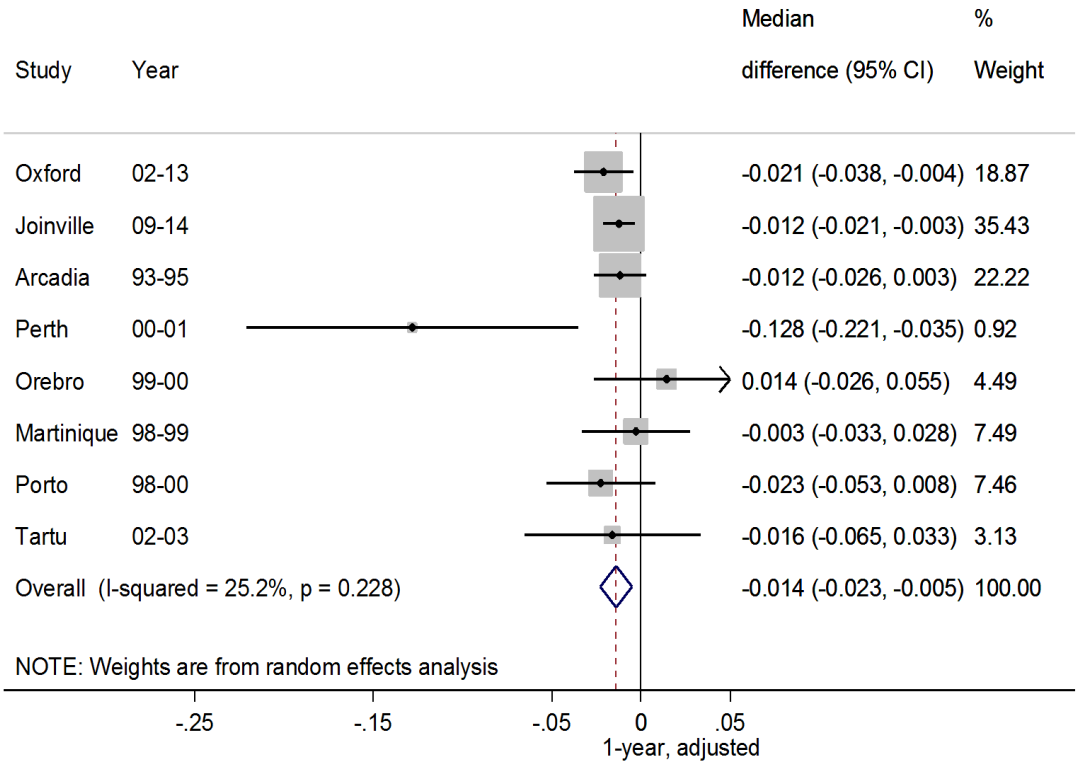
Supplemental Table C-11. Comparison of HRQoL subdomains among the AQoL, EQ5D-3L and SF36 (From Hawthorne et al 2001)[288]

HRQoL dimension	SF36	AQoL	EQ5D-3L
Relative to the body			
Anxiety/depression	***	*	*
Bodily care	*	*	*
General health	******		
Mobility	***	*	*
Pain	**	*	*
Physical ability/vitality	******		
Rest and fatigue	**	*	
Sensory function		**	
Cognition	-		
Memorys	-		
Social expression			
Activity of daily living		*	*
Communication		*	
Emotional fulfilment	**		
Family role		*	
Intimacy/isolation		*	
Medical aid use		*	
Medical treatment		**	
Social function	**	*	
Work function	**		
Sexual relationship	-		

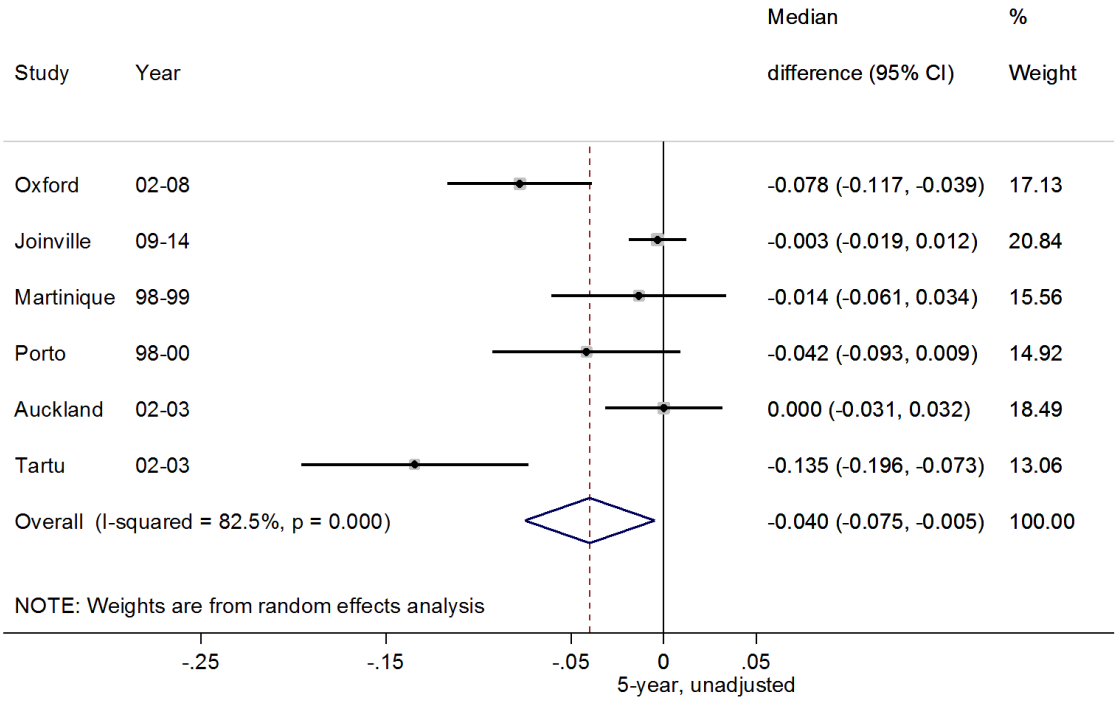
AQoL=Assessment of Quality of Life;[195] EQ5D=European Quality of Life–5 Dimensions;[194] SF36=Short form–36 questions[266]

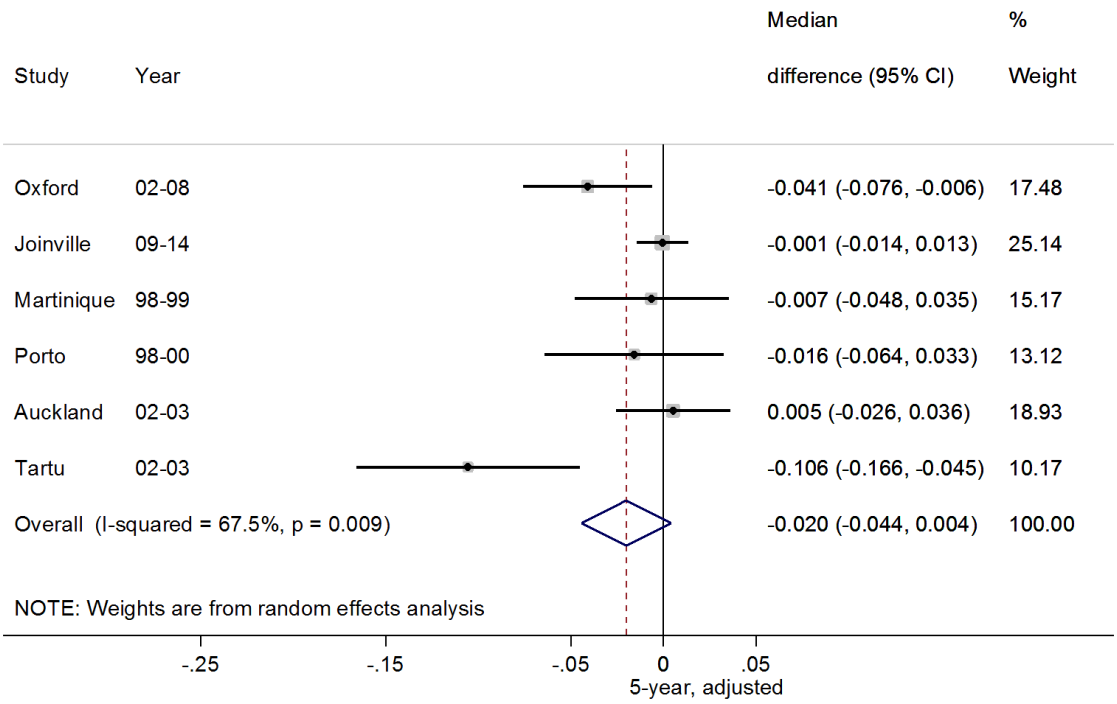
More asterisks (*) denote a greater coverage of HRQoL instrument across important dimensions





Supplementary Figure C-1. Median difference in EQ5D utility scores mapped from the modified Rankin Scale for women compared to men at 1 year after stroke in unadjusted (top panel) and adjusted (bottom panel) models from eight studies.





Supplementary Figure C-2. Median difference in EQ5D utility scores mapped from the modified Rankin Scale for women compared to men at 5 years after stroke in unadjusted (top panel) and adjusted (bottom panel) models from five studies.

Appendix D: Sex differences in severity of stroke in the INternational STRoke oUtComes sTudy: a meta-analysis of individual participant data

Supplemental Table D-1a. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Oxford, Joinville, Melbourne and Perth

Characteristic	Oxford				Joinville				Melbourne				Perth			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Number of cases	550	537	48	46	780	714	129	94	357	387	73	71	61	62	8	7
SOCIODEMOGRAPHIC																
Mean (SD) Age	**72.4 (12.0)**	**77.7 (12.1)**	69.5 (14.3)	73.5 (16.2)	**63.5 (12.5)**	**66.8 (15.7)**	**58.2 (15.4)**	**62.5 (15.5)**	**72.4 (12.7)**	**76.3 (14.3)**	**70.3 (13.5)**	**75.2 (15.2)**	74.0 (12.5)	78.0 (10.1)	68.0 (18.5)	73.5 (12.3)
Race (%)																
Caucasian	-	-	-	-	-	-	-	-	93.0	94.6	91.8	93.0	-	-	-	-
Non-Caucasian									3.4	2.8	4.1	5.6				
Unknown									3.6	2.6	4.1	1.4				
Marital status (%)																
Single/widowed	**23.6**	**54.0**	12.5	39.1	-	-	-	-	-	-	-	-	**64.0**	**37.1**	87.5	57.1
Married	**65.3**	**34.6**	62.5	54.4									**32.8**	**58.1**	12.5	42.9
Unknown	**11.1**	**11.4**	25.0	6.5									**3.3**	**4.8**	0.0	0.0
Education level (%)																
≤ Grade 12	**65.1**	**66.5**	47.9	60.9	93.9	93.7	93.8	95.7	**51.3**	**56.1**	**39.7**	**47.9**	-	-	-	-
> Grade 12	**15.6**	**9.1**	8.3	6.5	5.8	5.6	6.2	3.2	**43.4**	**42.4**	**53.4**	**52.1**				
Unknown	**19.3**	**24.4**	43.8	32.6	0.4	0.7	0.0	1.1	**5.3**	**1.6**	**6.9**	**0.0**				
Social class (%)																
Professional	**17.1**	**6.5**	**6.3**	**4.4**	-	-	-	-	**38.7**	**32.8**	**38.4**	**42.3**	**21.3**	**3.2**	12.5	0.0
Non-manual	**21.8**	**27.9**	**20.8**	**47.8**					**10.4**	**14.2**	**16.4**	**9.9**	**6.6**	**12.9**	0.0	0.0
Manual	**41.1**	**35.9**	**35.4**	**19.6**					**43.7**	**35.9**	**38.4**	**25.4**	**21.3**	**15.8**	50.0	14.3
Unknown	**20.0**	**29.6**	**37.5**	**28.3**					**7.3**	**17.1**	**6.9**	**22.5**	**50.8**	**58.1**	37.5	85.7
PRE-STROKE HEALTH																
Modified Rankin Score (%)																
0-2	**85.8**	**73.6**	79.2	69.6	-	-	-	-	-	-	-	-	82.0	67.7	12.5	14.3
3-5	**13.6**	**25.1**	10.4	26.1									16.4	24.2	75.0	71.4
Unknown	**0.6**	**1.3**	10.4	4.4									1.6	8.1	12.5	14.3
Institutional residence (%)																
Yes	-	-	-	-	-	-	-	-	**6.4**	**13.2**	6.9	15.5	4.9	9.7	62.5	14.3
No									**93.3**	**86.3**	91.8	84.5	95.1	90.3	12.5	42.9
Unknown									**0.3**	**0.5**	1.4	0.0	0.0	0.0	25.0	42.9
Barthel Index (%)																
20	-	-	-	-	-	-	-	-	**60.2**	**49.6**	54.8	36.6	-	-	-	-
<20									**13.5**	**19.6**	6.9	14.1				
Unknown									**26.3**	**30.8**	38.4	49.3				
MEDICAL HISTORY																
Atrial fibrillation (%)																
Yes	21.1	25.5	16.7	10.9	4.6	6.0	0.0	1.1	22.4	26.6	12.3	11.3	19.7	24.2	0.0	28.6
No	78.9	74.3	83.3	89.1	95.4	94.0	100.0	98.9	77.0	73.1	84.9	88.7	75.4	74.2	75.0	71.4
Unknown	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.9	1.6	0.0	0.0
Hypertension (%)																
Yes	61.3	66.7	54.2	47.8	**65.8**	**72.6**	69.0	77.7	53.2	58.9	53.4	64.8	54.1	61.3	37.5	42.9
No	38.7	33.3	41.7	52.2	**34.2**	**27.5**	31.0	22.3	45.9	40.6	45.2	35.2	41.0	38.7	37.5	57.1
Unknown	0.0	0.0	4.2	0.0	**0.0**	**0.0**	0.0	0.0	0.8	0.5	1.4	0.0	4.9	0.0	25.0	0.0
Ischaemic heart disease (%)																
Yes	**16.2**	**9.3**	8.3	0.0	**7.6**	**3.5**	3.1	1.1	16.8	14.0	**15.8**	**2.8**	18.0	8.1	12.5	0.0
No	**83.5**	**90.7**	83.3	97.8	**92.4**	**96.5**	96.9	98.9	82.6	85.8	**83.6**	**97.2**	78.7	88.7	62.5	100.0

Supplemental Table D-1a. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Oxford, Joinville, Melbourne and Perth

Characteristic	Oxford				Joinville				Melbourne				Perth			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Unknown	**0.4**	**0.0**	8.3	2.2	**0.0**	**0.0**	0.0	0.0	0.6	0.3	**1.4**	**0.0**	3.3	3.2	25.0	0.0
Peripheral vascular disease (%)																
Yes	9.1	5.6	2.1	0.0	-	-	-	-	**12.6**	**5.7**	6.9	2.8	-	-	-	-
No	90.7	94.2	97.9	100.0					**86.8**	**94.1**	91.8	95.8				
Unknown	0.2	0.2	0.0	0.0					**0.6**	**0.3**	1.4	1.4				
Transient ischaemic attack (%)																
Yes	14.4	11.9	10.4	10.9	2.6	2.4	3.9	0.0	9.8	9.8	8.2	5.6	21.3	11.3	12.5	14.3
No	85.6	87.9	89.6	89.1	97.4	97.6	96.1	100.0	89.6	89.7	89.0	94.4	67.2	80.7	50.0	85.7
Unknown	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.5	2.7	0.0	11.5	8.1	37.5	0.0
Diabetes (%)																
Yes	15.6	12.1	8.3	8.7	-	-	-	-	19.9	18.4	9.6	4.2	24.6	21.0	0.0	14.3
No	84.4	87.9	91.7	91.3					79.6	91.7	90.4	95.8	75.4	79.0	75.0	85.7
Unknown	0.0	0.0	0.0	0.0					0.6	0.0	0.0	0.0	0.0	0.0	25.0	0.0
Dementia (%)																
Yes	-	-	-	-	-	-	-	-	**4.5**	**9.3**	**4.1**	**15.5**	-	-	-	-
No									**81.8**	**78.3**	**84.9**	**81.7**				
Unknown									**13.7**	**124**	**11.0**	**2.8**				
Smoking (%)																
Current	**17.5**	**13.8**	**20.8**	**4.4**	**29.6**	**13.2**	**34.9**	**59.6**	**20.2**	**13.7**	**16.4**	**9.9**	**11.5**	**4.8**	25.0	0.0
Former	**53.5**	**28.3**	**39.6**	**28.3**	**41.3**	**18.6**	**34.1**	**25.5**	**46.2**	**22.5**	**53.4**	**19.7**	**52.5**	**14.5**	25.0	14.3
Never	**28.4**	**56.4**	**27.1**	**56.5**	**29.1**	**68.2**	**31.0**	**14.9**	**29.4**	**55.0**	**23.3**	**52.1**	**18.0**	**53.2**	25.0	42.9
Unknown	**0.7**	**1.5**	**12.5**	**10.9**	**0.0**	**0.0**	**0.0**	**0.0**	**4.2**	**8.8**	**6.9**	**18.3**	**18.0**	**27.4**	25.0	42.9
Alcohol use (%)																
Non-drinkers	**28.6**	**57.0**	**16.7**	**41.3**	**49.0**	**83.1**	**19.4**	**2.1**	**20.2**	**46.0**	**15.1**	**35.2**	27.9	30.7	25.0	28.6
Not heavy drinkers	**63.8**	**34.6**	**45.8**	**32.6**	**38.7**	**15.8**	**34.9**	**18.1**	**56.3**	**41.3**	**53.4**	**38.0**	9.8	14.5	0.0	0.0
Heavy drinkers	**3.3**	**1.7**	**8.3**	**2.2**	**13.3**	**1.1**	**45.7**	**79.8**	**8.2**	**1.3**	**12.3**	**1.4**	29.5	17.7	37.5	0.0
Ex-drinkers	-	-	-	-	-	-	-	-	**8.7**	**1.3**	**11.0**	**2.8**	6.6	1.6	0.0	0.0
Unknown	**4.4**	**6.7**	**29.2**	**23.9**	**0.0**	**0.0**	0.0	0.0	**6.7**	**10.1**	**8.2**	**22.5**	26.2	35.5	37.5	0.0
Mean (SD) Body mass index	26.4 (4.6)	26.2 (5.8)	25.3 (3.4)	23.2 (7.5)	26.7 (4.2)	26.9 (5.5)	27.0 (4.8)	25.8 (5.0)	-	-	-	-	25.9 (4.0)	25.0 (4.0)	-	-
Medication																
Antihypertensives (%)																
Yes	-	-	-	-	**61.2**	**69.5**	**55.0**	**69.2**	53.3	61.8	41.1	49.3	45.9	56.5	37.5	42.9
No					**38.9**	**30.5**	**45.0**	**30.9**	46.2	38.0	57.5	50.7	47.5	40.3	37.5	57.1
Unknown					**0.0**	**0.0**	**0.0**	**0.0**	0.3	0.3	1.4	0.0	6.6	3.2	25.0	0.0
Antiplatelet (%)																
Yes	-	-	-	-	30.1	33.6	20.9	24.5	30.5	30.5	20.6	28.2	**29.5**	**43.6**	25.0	42.9
No					69.9	66.4	79.1	75.5	69.2	69.5	78.1	71.9	**70.5**	**51.6**	62.5	57.1
Unknown					0.0	0.0	0.0	0.0	0.3	0.0	1.4	0.0	**0.0**	**4.8**	12.5	0.0
STROKE-RELATED FACTORS																
Hospital admission (%)	82.7	83.1	100.0	97.8	100.0	100.0	100.0	100.0	98.0	99.0	100.0	98.6	77.1	83.9	100.0	57.1
Ischaemic stroke subtype																
Atherothrombotic	-	-	-	-	27.9	26.0	-	-	23.8	18.1	-	-	-	-	-	-
Cardioembolic					27.4	28.4			26.3	25.3						
Lacunar					22.4	18.3			19.1	13.2						
Other Causes					22.2	27.3			1.1	1.6						
Undetermined					0.0	0.0			29.7	41.9						
Time to hospital† (%)																
≤ 4.5 hours	-	-	-	-	41.4	45.1	57.4	64.9	-	-	-	-	14.9	19.2	25.0	0.0
> 4.5 – 24 hours					27.7	24.7	24.8	20.2					8.5	13.5	12.5	0.0
> 24 hours					28.6	26.9	14.7	11.7					10.6	19.2	0.0	25.0
Unknown					2.3	3.4	3.1	3.2					66.0	18.1	62.5	75.0

Supplemental Table D-1a. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Oxford, Joinville, Melbourne and Perth

Characteristic	Oxford				Joinville				Melbourne				Perth			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women

Bold denotes statistically significant differences between men and women; IS, Ischaemic stroke; ICH, intracerebral haemorrhage; † among hospitalised patients

Supplemental Table D-1b. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Orebro, Dijon, Mãtao and Tartu

Characteristic	Orebro				Dijon				Mãtao				Tartu			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Number of cases	125	149	25	19	568	670	92	105	41	26	8	3	121	178	27	28
SOCIODEMOGRAPHIC																
Mean (SD) Age	**73.1 (10.5)**	**77.1 (10.7)**	71.9 (11.5)	75.6 (9.9)	**71.7 (15.3)**	**77.2 (15.8)**	**71.0 (15.8)**	**76.6 (18.3)**	65.1 (12.3)	64.5 (12.6)	62.9 (7.0)	68.7 (7.5)	**68.1 (10.9)**	**75.6 (10.9)**	63.6 (15.9)	68.1 (12.6)
Marital status (%)																
Single/widowed	**32.8**	**36.9**	**32.0**	**63.2**	-	-	-	-	26.8	38.5	25.0	66.7	-	-	-	-
Married	**67.2**	**61.7**	**68.0**	**36.8**					68.3	61.5	75.0	0.0				
Unknown	**0.0**	**0.0**	**0.0**	**0.0**					4.8	0.0	0.0	33.3				
Education level (%)																
≤ Grade 12	-	-	-	-	-	-	-	-	80.5	96.2	75.0	33.3	-	-	-	-
> Grade 12									7.3	3.9	25.0	0.0				
Unknown									12.2	0.0	0.0	66.7				
PRE-STROKE HEALTH																
Modified Rankin Score (%)																
0-2	-	-	-	-	-	-	-	-	-	-	-	-	87.6	87.1	85.2	82.1
3-5													4.1	7.9	3.7	3.6
Unknown													8.3	5.1	11.1	14.3
Institutional residence (%)																
Yes	**2.4**	**9.4**	4.0	21.1	**3.5**	**10.8**	4.4	6.7	-	-	-	-	-	-	-	-
No	**97.6**	**90.6**	96.0	79.0	**96.5**	**89.3**	95.7	93.3								
Unknown	**0.0**	**0.0**	0.0	0.0	**0.0**	**0.0**	0.0	0.0								
Barthel Index (%)																
20	76.0	65.1	4.0	47.4	-	-	-	-	-	-	-	-	-	-	-	-
<20	6.4	7.4	68.0	5.3												
Unknown	17.6	27.5	28.0	47.4												
MEDICAL HISTORY																
Atrial fibrillation (%)																
Yes	20.8	26.2	24.0	5.3	14.6	19.0	11.9	20.2	2.4	0.0	0.0	0.0	30.6	41.6	7.4	7.1
No	79.2	73.8	76.0	94.7	85.3	80.4	88.1	79.8	90.2	100	100	66.7	69.4	58.4	92.6	92.9
Unknown	0.0	0.0	0.0	0.0	0.2	0.6	0.0	0.0	7.3	0.0	0.0	33.3	0.0	0.0	0.0	0.0
Hypertension (%)																
Yes	31.2	42.3	32.0	31.6	66.2	70.6	68.3	64.9	63.4	69.2	87.5	66.7	55.4	71.4	63.0	71.4
No	67.2	55.7	68.0	68.4	33.6	28.8	31.7	35.1	31.7	30.8	12.5	0.0	44.6	28.7	37.0	28.6
Unknown	1.6	2.0	0.0	0.0	0.2	0.6	0.0	0.0	4.9	0.0	0.0	33.3	0.0	0.0	0.0	0.0
Ischaemic heart disease (%)																
Yes	19.2	14.8	8.0	0.0	16.3	12.7	8.9	7.0	2.4	11.5	12.5	0.0	38.0	43.8	22.2	32.1
No	80.8	85.2	92.0	100.0	93.5	86.7	91.1	93.0	90.2	88.5	87.5	66.7	62.0	56.2	77.8	67.9
Unknown	0.0	0.0	0.0	0.0	0.2	0.6	0.0	0.0	7.3	0.0	0.0	33.3	0.0	0.0	0.0	0.0

Supplemental Table D-1b. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Orebro, Dijon, Mãtao and Tartu

Characteristic	Orebro				Dijon				Mãtao				Tartu			
	IS		ICH		IS		ICH		IS		ICH		IS		ICH	
Peripheral vascular disease (%)																
Yes	37.6	26.9	28.0	21.1	**7.7**	**4.5**	5.9	5.3	-	-	-	-	-	-	-	-
No	62.4	72.5	78.0	79.0	**92.1**	**94.9**	94.1	94.7								
Unknown	0.0	0.7	0.0	0.0	**0.2**	**0.6**	0.0	0.0								
Transient ischaemic attack (%)																
Yes	20.0	13.4	4.0	10.5	6.6	8.8	5.9	3.5	9.8	3.9	0.0	0.0	7.4	8.4	0.0	0.0
No	80.0	86.6	96.0	89.5	93.3	91.2	94.1	96.5	82.9	93.2	100.0	33.3	92.6	91.6	100.0	100.0
Unknown	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.3	0.0	0.0	33.3	0.0	0.0	0.0	0.0
Diabetes (%)																
Yes	20.8	16.1	8.0	10.5	-	-	-	-	-	-	-	-	-	-	-	-
No	78.4	81.9	92.0	89.5												
Unknown	0.8	2.0	0.0	0.0												
Dementia (%)																
Yes	4.8	10.1	8.0	10.5	-	-	-	-	-	-	-	-	-	-	-	-
No	85.2	89.9	92.0	89.5												
Unknown	0.0	0.0	0.0	0.0												
Smoking (%)																
Current	**29.6**	**18.1**	24.0	10.5	**47.0**	**81.7**	**59.4**	**82.5**	**43.9**	**19.2**	50.0	33.3	-	-	-	-
Former	**-**	**-**	-	-	**23.2**	**2.5**	**15.8**	**2.6**	**-**	**-**	-	-				
Never	**63.2**	**79.2**	64.0	79.0	**27.3**	**12.3**	**21.8**	**9.7**	**51.2**	**80.8**	50.0	33.3				
Unknown	**7.2**	**2.7**	12.0	10.5	**2.6**	**3.5**	**3.0**	**2.3**	**4.9**	**0.0**	0.0	33.3				
Alcohol use (%)																
Non-drinkers	-	-	-	-	86.6	95.6	77.1	95.6	**70.7**	**100.0**	75.0	33.3	-	-	-	-
Current drinkers*					11.5	2.3	20.8	3.5	**22.0**	**0.0**	25.0	33.3				
Ex-drinkers					-	-	-	-	**-**	**-**	-	-				
Unknown					1.9	2.1	2.0	0.9	**7.3**	**0.0**	0.0	33.3				
STROKE-RELATED FACTORS																
Hospital admission (%)	95.2	96.0	92.0	94.7	99.7	100.0	100.0	99.1	100.0	100.0	100.0	100.0	98.4	99.4	100.0	100.0
Ischaemic stroke subtype																
Atherothrombotic	54.4	55.7	-	-	-	-	-	-	-	-	-	-	28.9	25.8	-	-
Cardioembolic	12.8	14.1											28.1	39.3		
Lacunar	30.4	26.9											30.6	23.0		
Other Causes	1.6	1.3											12.4	10.7		
Undetermined	0.8	2.0											0.0	1.1		
Time to arrive hospital† (%)																
≤ 4.5 hours	-	-	-	-	-	-	-	-	-	-	-	-	30.3	32.2	59.3	57.1
> 4.5 – 24 hours													6.7	5.1	3.7	0.0
> 24 hours													2.5	2.8	0.0	0.0
Unknown													60.5	59.9	37.0	42.8

Supplemental Table D-1b. Characteristics of included cohort studies by sex among patients with NIHSS data, for studies conducted in Orebro, Dijon, Mãtao and Tartu

Characteristic	Orebro		Dijon		Mãtao		Tartu	
	IS	ICH	IS	ICH	IS	ICH	IS	ICH

Bold denotes statistically significant differences between men and women; IS, Ischaemic stroke; ICH, intracerebral haemorrhage; † among hospitalised patients

Supplemental Table D-2. Severity of ischaemic stroke by subtype among women and men

Study	Number of cases (%)		NIHSS, mean (IQR)		NIHSS>7, n (%)		More severe stroke
	Men	Women	Men	Women	Men	Women	RR (95% CI)
Large-artery atherosclerosis							
Joinville	247 (56.0%)	194 (44.0%)	4.0 (2.0-9.0)	5.0 (2.0-12.0)	74/247 (30.0%)	73/194 (37.6%)	1.26 (0.97-1.63)
Melbourne	85 (23.8%)	70 (45.2%)	4.0 (1.0-8.0)	4.0 (2.0-14.0)	22/85 (25.9%)	29/70 (41.4%)	**1.60 (1.01-2.53)**
Orebro	68 (45.0%)	83 (55.0%)	3.0 (2.0-10.5)	6.0 (3.0-10.0)	20/68 (29.4%)	34/83 (41.0%)	1.39 (0.89-2.19)
Tartu	35 (43.2%)	46 (56.8%)	12.0 (6.0-20.0)	13.0 (7.0-19.0)	22/35 (62.9%)	33/46 (71.7%)	1.14 (0.93-1.56)
Pooled	435 (52.5%)	393 (47.5%)	4.0 (2.0-10.0)	6.0 (3.0-13.0)	138/435 (31.7%)	169/393 (43.0%)	**1.32 (1.05-1.66)***
Cardioembolism							
Joinville	259 (47.3%)	289 (52.7%)	5.0 (2.0-12.0)	8.0 (3.0-16.0)	100/259 (38.6%)	150/289 (51.9%)	**1.34 (1.11-1.63)**
Melbourne	94 (49.0%)	98 (51.0%)	7.5 (4.0-14.0)	9.5 (5.0-17.0)	47/94 (50%)	58/98 (59.2%)	1.18 (0.91-1.54)
Orebro	16 (43.2%)	21 (56.8%)	4.0 (2.0-7.0)	12.0 (4.0-20.0)	4/16 (25.0%)	13/21 (61.9%)	2.48 (0.98-6.25)
Tartu	34 (32.7%)	70 (67.3%)	8.5 (4.0-20.0)	12.5 (4.0-20.0)	18/34 (52.9%)	43/70 (61.4%)	1.16 (0.80-1.68)
Pooled	403 (45.7%)	478 (54.3%)	6.0 (3.0-13.0)	9.0 (3.0-17.0)	169/403 (41.9%)	264/478 (55.2%)	**1.32 (1.08-1.60)***
Small-vessel occlusion							
Joinville	247 (56.5%)	190 (43.5%)	3.0 (2.0-4.0)	2.0 (1.0-5.0)	17/247 (6.9%)	20/190 (10.5%)	1.53 (0.82-2.84)
Melbourne	68 (57.1%)	51 (42.9%)	3.0 (2.0-4.0)	2.0 (1.0-5.0)	3/68 (4.4%)	6/51 (11.8%)	2.67 (0.70-10.2)
Orebro	38 (48.7%)	40 (51.3%)	4.0 (3.0-5.0)	3.0 (2.0-4.0)	2/38 (5.3%)	2/40 (5.0%)	0.95 (0.14-6.49)
Tartu	37 (47.4%)	41 (52.6%)	0.0 (0.0-3.0)	2.0 (0.0-8.0)	1/37 (2.7%)	11/41 (26.8%)	**9.93 (1.33-74.2)**
Pooled	390 (54.8%)	322 (45.2%)	3.0 (2.0-4.0)	3.0 (1.0-5.0)	23 (5.9%)	39 (12.1%)	**2.05 (1.23, 3.44)***
Other aetiology							
Joinville	27 (39.7%)	41 (60.3%)	2.0 (1.0-8.0)	2.0 (1.0-6.0)	7/27 (25.9%)	10/41 (24.4%)	0.94 (0.41-2.18)
Melbourne	4 (40.0%)	6 (60.0%)	4.0 (1.5-8.5)	5.0 (1.0-10.0)	1/4 (25%)	2/6 (33.3%)	1.33 (0.16-11.5)
Orebro	2 (50.0%)	2 (50.0%)	7.5 (6.0-9.0)	14.5 (5.0-24.0)	1/2 (50.0%)	1/2 (50.0%)	1.00 (0.10-9.61)
Tartu	15 (44.1%)	19 (55.9%)	5.0 (0.0-7.0)	5.0 (1.0-15.0)	3/15 (20.0%)	9/19 (47.4%)	2.37 (0.76-7.36)
Pooled	48 (41.4%)	68 (58.6%)	3.0 (1.0-7.5)	3.0 (1.0-10.0)	12/48 (25.0%)	22/68 (32.4%)	1.29 (0.64-2.61)*
Undetermined							
Joinville	-	-	-	-	-	-	-
Melbourne	106 (39.6%)	162 (60.5%)	5.0 (2.0-11.0)	4.0 (2.0-10.0)	39/106 (36.8%)	55/162 (34.0%)	0.92 (0.66-1.28)
Orebro	1 (25.0%)	3 (75.0%)	28.0 (NA)	3.0 (0.0-6.0)	1/1 (100%)	0/3 (0%)	NA
Tartu	0 (0.0%)	1 (100%)	-	7.5 (3.0-12.0)	0/0 (0%)	1/2 (50.0%)	NA
Pooled	107 (39.1%)	167 (61.0%)	5.0 (2.0-11.0)	4.0 (2.0-10.0)	40/107 (37.4%)	56 (33.5%)	0.90 (0.60-1.35)*

National Institutes of Health Stroke Scale=NIHSS; Bold denotes statistically significant differences between men and women

*RR was pooled using log-binominal regression with random-effects

Supplemental Table D-3. List of covariates not meeting the criteria for confounding factors of sex difference in severity (NIHSS) of ischaemic stroke

Study	Covariates
Oxford	SEP, education, hypertension, AF, IHD, PVD, TIA, diabetes, BMI, smoking, marital status, alcohol, hospital admission,
Joinville	Stroke subtype, race, hypertension, AF, PVD, TIA, BMI, smoking, hospital admission (100%), pre-stroke medication (antihypertensives, antiplatelets, anticoagulants), delay to hospital, IHD, alcohol
Melbourne	Stroke subtype, race, SEP, education, hypertension, IHD, PVD, TIA, diabetes, smoking, alcohol, hospital admission, pre-stroke medication (antiplatelets, anticoagulants, antihypertensives), institutional residence
Perth	SEP, hypertension, AF, IHD, TIA, diabetes, smoking, alcohol, delay to hospital, pre-stroke medication (antihypertensives, antiplatelets), institutional residence, pre-stroke Barthel, hospital admission
Orebro	Stroke subtype, age†, marital status, hypertension, AF, IHD, PVD, TIA, diabetes, dementia, pre-stroke Barthel, hospital admission, smoking
Dijon	Hypertension, IHD, PVD, TIA, alcohol, hospital admission, institutional residence
Matão	Race, marital status, education, age†, hypertension, AF, IHD, PVD, TIA, smoking, alcohol, hospital admission
Tartu	Stroke subtype, hypertension, AF, IHD, TIA, hospital admission, delay to hospital, pre-stroke medication (antihypertensives, antiplatelets)

AF, Atrial fibrillation; BMI, body mass index; IHD, ischaemic heart disease; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease, TIA, transient ischaemic attack; SEP, socioeconomic position.

* Not meeting all 4 criteria (missing <20% of cases, associated with sex, associated with stroke severity, and the inclusion of the covariate changed the magnitude of the sex coefficient by ≥10%) but to be included in the final multivariable model

Supplemental Table D-4a. Analyses of heterogeneity in the sex differences in stroke severity (NIHSS>7) among eight population-based studies

	No of studies	Unadjusted				Adjusted for covariates*			
		I^2 (%)	P^H	RR(95% CI)	$P^{sub\text{-}group}$	I^2 (%)	P^H	RR(95% CI)	$P^{sub\text{-}group}$
Ischaemic stroke									
Geographic region									
Australasia	2	0.0	0.444	**1.23 (1.02-1.48)**	0.565	0.0	0.203	1.07 (0.89-1.29)	0.465
Europe	4	0.0	0.533	**1.36 (1.21-1.52)**		0.0	0.327	1.13 (0.97-1.32)	
South America	2	0.0	0.925	**1.41 (1.22-1.64)**		0.0	0.902	**1.28 (1.10-1.50)**	
Pre-stroke function									
Unavailable	2	0.0	0.515	**1.43 (1.24-1.64)**	0.334	12.4	0.336	1.10 (0.98-1.23)	0.139
Available	6	0.0	0.718	**1.30 (1.18-1.44)**		0.0	0.885	**1.27 (1.10-1.46)**	
Intracerebral haemorrhagic stroke									
Geographic region									
Australasia	2	0.0	0.958	1.26 (0.97-1.63)	0.515	0.0	0.948	1.21 (0.97-1.20)	0.503
Europe	4	0.0	0.728	1.05 (0.89-1.24)		0.0	0.832	1.07 (0.91-1.26)	
South America	2	0.0	0.759	1.05 (0.88-1.25)		0.0	0.778	1.03 (0.87-1.24)	
Pre-stroke function									
Unavailable	2	0.0	0.665	1.12 (0.97-1.30)	0.483	0.0	0.779	1.12 (0.97-1.30)	0.549
Available	6	0.0	0.935	1.04 (0.88-1.22)		0.0	0.983	1.03 (0.87-1.21)	

Bold denotes statistically significant differences between men and women; NIHSS, National Institutes of Health Stroke Scale; P^H, P-value of heterogeneity; RR (95% CI), relative risk (95% confidence interval) of having more severe stroke (NIHSS>7) for women compared to men

Supplemental Table D-4b. Testing the interactions between sex and two covariates: age and time period using a single pooled individual participant dataset in stroke severity

	Unadjusted			Adjusted for age		
Covariates	**RR***	**(95% CI)**	**$P_{interaction}$**	**RR**	**(95% CI)**	**$P_{interaction}$**
Ischaemic stroke						
Age (continuous)	1.35	(0.69-2.64)	0.793			
Age group						
≤65 years	1.19	(0.92-1.53)	Ref	-		
>65-75 years	**1.23**	**(1.00-1.52)**	0.855	-		
>75 years	**1.25**	**(1.11-1.41)**	0.705	-		
Year of stroke occurrence						
1996-2011 (continuous)	**1.26**	**(1.15-1.41)**	0.067	**1.15**	**(1.03- 1.29)**	0.128
Intracerebral haemorrhagic stroke						
Age (continuous)	0.85	(0.52-1.39)	0.324			
Age group						
≤65 years	1.00	(0.86-1.16)	Ref	-		
>65-75 years	**1.14**	**(0.97-1.33)**	0.360	-		
>75 years	**1.13**	**(1.03-1.24)**	0.136	-		
Year of stroke occurrence						
1996-2011 (continuous)	**1.16**	**(0.99, 1.36)**	**0.264**	**1.16**	**(1.09-1.22)**	0.281

Ref, Reference group

* RR (95% CI), female:male relative risk (95% confidence interval) of more severe stroke (NIHSS>7)

Supplemental Table D-5. Sensitivity analyses of difference in National Institutes of Health Stroke Scale (NIHSS) continuous scores between women and men

Study	N*	Unadjusted	Adjusted for		
			Age	Pre-stroke dependency	All confounding factors
		MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)
Ischaemic stroke					
Oxford	1077	**0.834 (0.265, 1.404)**	0.391 (-0.177, 0.959)	0.478 (-0.089, 1.045)	0.247 (-0.228, 0.722)
Joinville	1494	**0.856 (0.278, 1.434)**	**0.607 (0.038, 1.176)**	---	**0.607 (0.038, 1.176)**
Melbourne	647	**1.171 (0.190, 2.152)**	0.697 (-0.260, 1.654)	**1.141 (0.190, 2.091)**	0.645 (-0.334, 1.625)
Perth	123	-0.466 (-2.893, 1.960)	-1.162 (-3.596, 1.215)	-0.681 (-3.240, 1.876)	-1.162 (-3.596, 1.215)
Orebro	274	1.220 (-0.029, 2.469)	1.102 (-0.196, 2.373)	1.021 (-0.210, 2.252)	0.853 (-0.278, 1.984)
Dijon	1238	**1.130 (0.467, 1.794)**	0.640 (-0.017, 1.297)	**0.086 (0.213, 1.500)**	0.018 (-0.703, 0.7381)
Mătao	67	**3.330 (0.095, 6.564)**	**3.337 (0.078, 6.595)**	---	**3.337 (0.078, 6.595)**
Tartu	280	**2.477 (0.742, 4.213)**	1.182 (-0.619, 2.983)	**1.729 (0.078, 3.380)**	1.122 (-0.911, 2.900)
Pooled	5,200	**1.011 (0.700, 1.323)**	**0.601 (0.296, 0.905)**	**0.802 (0.440, 1.164)**	**0.426 (0.095, 0.757)**
Intracerebral haemorrhage					
Oxford	223	1.996 (-1.661, 5.654)	1.96 (-1.748, 5.671)	---	---
Joinville	94	0.207 (-2.380, 2.793)	-0.118 (-2.718, 2.482)	---	---
Melbourne	114	**4.139 (0.598, 7.680)**	**3.572 (0.014, 7.129)**	---	---
Perth	15	1.932 (-10.391, 14.257)	1.081 (-11.677, 13.840)	---	---
Orebro	44	2.912 (-2.450, 8.276)	3.751 (-1.649, 9.150)	---	---
Dijon	197	0.914 (-1.579, 3.406)	0.460 (-2.044, 2.964)	---	---
Mătao	11	6.046 (-9.800, 21.891)	0.627 (-10.243, 25.496)	---	---
Tartu	55	-0.828 (-5.104, 3.449)	-0.706 (-5.074, 3.662)	---	---
Pooled	753	**1.654 (0.188, 3.120)**	1.452 (-0.027, 2.931)		

Bold denotes statistically significant results; MD=mean difference

Appendix E: Sex differences in care and long-term mortality after stroke: Australian Stroke Clinical Registry

Supplemental Table E-1. Sensitivity analyses of receiving medications among those without aspirin within 48 hours in the subset of Queensland data

Medication	Men		Women		
	n	(%)	n	%	P-value
Died within 48 hours					
No	711	(96.2%)	755	(95.3%)	0.392
Yes	28	(3.8%)	37	(4.7%)	
Antiplatelets or antithrombotics at discharge					
No	293	(51.4%)	311	(54.4%)	0.315
Yes	277	(48.6%)	261	(45.6%)	
Thrombolysis therapy					
No	592	(85.3%)	643	(88.6%)	0.068
Yes	102	(14.7%)	83	(11.4%)	

Supplemental Table E-2. Sex differences in mortality up to 1 year after stroke in univariate (unadjusted) and bivariate models (adjusting for single covariates that differ by sex)

	7 days				30 days				1 year			
	MRR	95%	CI	Δ (%)*	MRR	95%	CI	Δ (%)*	MRR	95%	CI	Δ (%)*
Unadjusted	1.42	1.25	1.60		1.45	1.33	1.59		1.44	1.34	1.54	
Adjusted for												
Age	1.19	1.05	1.35	50%	1.15	1.05	1.27	63%	1.09	1.01	1.17	76%
Born in Australia	1.43	1.26	1.62	-2%	1.46	1.33	1.60	-1%	1.44	1.34	1.55	0%
Transfer from other hospital	1.41	1.25	1.60	2%	1.46	1.33	1.60	-1%	1.44	1.34	1.54	0%
Stroke severity (unable to walk on admission)	1.24	1.09	1.40	39%	1.29	1.18	1.41	42%	1.31	1.22	1.41	26%
Cause of stroke known (IS)	1.58	1.34	1.87	0%§	1.57	1.40	1.76	0%§	1.55	1.42	1.69	0%§
Discharge to aged care†	1.47	0.92	2.34	16%§	1.39	1.15	1.69	29%§	1.31	1.18	1.45	23%§
Length of stay†	1.56	0.99	2.46	-30%§	1.63	1.34	1.97	-4%§	1.40	1.26	1.54	5%§
Aspirin administration ≤48 hours (IS)‡	1.38	1.02	1.85	30%§	1.31	1.07	1.59	26%§	1.42	1.22	1.65	16%§

MRR, mortality rate ratio; CI, confidence interval; IS, ischaemic stroke

* % change of coefficient of sex difference between unadjusted and adjusted models was calculated by the formula (unadjusted β – adjusted β)/ unadjusted β *100

† among those discharged only

‡ among Queensland hospitals only

§ % change was calculated based on unadjusted and adjusted estimates of the relevant subgroup

Supplemental Table E-3. Sensitivity analyses of the role of missing data of confounders (age and severity) on mortality rate ratio at 30 days and 1 year after stroke for women compared to men with unadjusted and (n=50 imputations)

	Complete−case analysis			Imputed analysis		
	N	Unadjusted MRR (95% CI)	Adjusted MRR* (95% CI)	N	Unadjusted MRR (95% CI)	Adjusted MRR* (95% CI)
All hospitals						
At 7 days	13304	**1.42 (1.25-1.60)**	1.09 (0.96-1.24)	14118	**1.42 (1.25-1.60)**	1.09 (0.96-1.24)
At 30 days	13304	**1.45 (1.33, 1.59)**	1.07 (0.97, 1.17)	14118	**1.45 (1.33, 1.59)**	1.07 (0.97, 1.17)
At 1 year, **without interaction** with severity	13304	**1.44 (1.34, 1.54)**	1.03 (0.95, 1.10)	14118	**1.45 (1.35, 1.57)**	1.03 (0.95, 1.11)
At 1 year, unable to walk	8624	**1.36 (1.26, 1.47)**	1.05 (0.97, 1.14)	8626	**1.36 (1.26, 1.47)**	1.05 (0.97, 1.14)
At 1 year, able to walk	4680	0.99 (0.80, 1.22)	0.81 (0.65, 1.00)	4681	0.99 (0.80, 1.22)	0.81 (0.65, 1.00)
Queensland data						
At 7 days	4803	**1.22 (0.99, 1.50)**	0.93 (0.75, 1.16)	5224	**1.20 (0.98, 1.47)**	0.93 (0.75, 1.16)
At 30 days	4803	**1.26 (1.09, 1.47)**	0.89 (0.76, 1.03)	5224	**1.26 (1.10, 1.47)**	0.89 (0.76, 1.03)
At 1 year	4803	**1.32 (1.17, 1.49)**	0.90 (0.79, 1.01)	5224	**1.34 (1.19, 1.50)**	0.92 (0.82, 1.04)

MRR: mortality rate ratio; CI: confidence interval
* adjusted estimates for age and severity of stroke

Supplemental Table E-4. Sensitivity analyses of mortality rate ratio at 30 days and 1 year after stroke for women compared to men with excluding early deaths i.e. ≤7 days, ≤30 days, ≤90 days, or ≤180 days)

	Not excluding early deaths					Excluding early deaths						
		Unadjusted		Adjusted			Unadjusted		Adjusted		Excl. deaths	Confounders in adjusted models
	N	MRR	(95% CI)	MRR	(95% CI)	N	MRR	(95% CI)	MRR	(95% CI)		
At 30 days	13304	**1.45**	**(1.33, 1.59)**	1.07	(0.97, 1.17)	12285	**1.48**	**(1.29, 1.69)**	1.02	(0.89, 1.17)	≤7 days	Age, severity
At 1 year, unable to walk	8624	**1.36**	**(1.26, 1.47)**	1.05	(0.97, 1.14)	7632	**1.37**	**(1.25, 1.51)**	1.01	(0.91, 1.12)	≤30 days	Age
At 1 year, able to walk	4680	0.99	(0.80, 1.22)	0.81	(0.65, 1.00)	4653	0.98	(0.78, 1.22)	0.80	(0.64, 1.00)	≤30 days	Age
At 1 year, unable to walk	8624	**1.36**	**(1.26, 1.47)**	1.05	(0.97, 1.14)	6848	**1.37**	**(1.19, 1.56)**	0.99	(0.86, 1.14)	≤30 days	age
At 1 year, able to walk	4680	0.99	(0.80, 1.22)	0.81	(0.65, 1.00)	4575	0.91	(0.70, 1.17)	**0.75**	**(0.58, 0.98)**	≤30 days	age
At 1 year, unable to walk	8624	**1.36**	**(1.26, 1.47)**	1.05	(0.97, 1.14)	10967	**1.22**	**(1.02, 1.46)**	0.87	(0.73, 1.05)	≤90 days	age
At 1 year, able to walk	4680	0.99	(0.80, 1.22)	0.81	(0.65, 1.00)	4497	0.91	(0.67, 1.24)	0.75	(0.55, 1.02)	≤90 days	age
At 1 year, unable to walk	8624	**1.36**	**(1.26, 1.47)**	1.05	(0.97, 1.14)	6237	1.13	(0.89, 0.45)	0.81	(0.64, 1.05)	≤180 days	age
At 1 year, able to walk	4680	0.99	(0.80, 1.22)	0.81	(0.65, 1.00)	4408	0.80	(0.51, 1.28)	0.66	(0.42, 1.06)	≤180 days	age

MRR: mortality rate ratio; CI: confidence interval; Excl.: excluding

Supplemental Table E-5: Characteristic of AuSCR registrants among all hospitals, Queensland (21 hospitals) and non-Queensland (18 hospitals)

	All hospitals	Queensland	Non-Queensland	P−value*
	n (%)	n (%)	n (%)	
Number of cases	14118	5224	8894	
Sociodemographics				
Women	7580 (46.3%)	2405 (46.0%)	4133 (46.5%)	0.897
Age, median (IQR)†	75.1 (63.8−85.8)	73.8 (62.7−83.2)	75.8 (64.6−83.7)	0.107
Born in Australia†	9224 (65.3%)	3675 (70.4%)	5549 (62.4%)	0.311
Aboriginal or Torres Strait Islander†	206 (1.5%)	126 (2.4%)	80 (0.9%)	0.065
Socioeconomic status†				
IRSAD1 (most disadvantage)	2565 (18.2%)	1418 (27.1%)	1147 (12.9%)	0.610
IRSAD2	2922 (20.7%)	1033 (19.8%)	1889 (21.2%)	
IRSAD3	1766 (12.5%)	653 (12.5%)	1113 (12.5%)	
IRSAD4	2840 (20.1%)	1090 (20.9%)	1750 (19.7%)	
IRSAD5 (least disadvantage)	4023 (28.5%)	1030 (19.7%)	2993 (33.7%)	
Stroke−related factors				
Transfer from other hospital†	2040 (14.5%)	929 (17.9%)	1111 (12.5%)	0.910
In−hospital stroke†	774 (5.5%)	329 (6.3%)	445 (5.0%)	0.958
Time (minutes) from onset to arrival, median (IQR)§	186 (81−677)	181 (81−614)	190 (81−706)	0.762
Walking independently at admission‡	4681 (35.2%)	1645 (34.3%)	3036 (35.7%)	0.735
Cause of stroke known†	6964 (50.7%)	2727 (52.2%)	4272 (50.2%)	0.547
Type of stroke				
Intracerebral haemorrhagic	2234 (15.8%)	828 (15.9%)	1406 (15.8%)	0.958
Ischaemic stroke	11444 (81.1%)	4232 (81.0%)	7212 (81.1%)	
Undetermined	437 (3.1%)	164 (3.1%)	273 (3.1%)	
Discharge destination				
Died in hospital	1438 (10.2%)	500 (9.6%)	938 (10.6%)	0.999
Aged care	666 (4.7%)	233 (4.5%)	433 (4.9%)	
Home	5446 (38.6%)	1998 (38.3%)	3448 (38.8%)	
Rehabilitation	4320 (30.6%)	1274 (24.4%)	3046 (34.3%)	
Hospitals/other	2248 (15.9%)	1219 (23.3%)	1029 (11.6%)	
Length of stay†				
LOS if discharged, median (IQR) days	5 (3−10)	6 (3−10)	5 (3−10)	0.285
LOS if died in hospital, median (IQR)	6 (3−12)	6 (3−13)	6 (3−12)	1.000
LOS including death, median (IQR)	5 (3−10)	6 (3−10)	5 (3−10)	0.244
Evidence−based therapies				
Treated in stroke unit	11513 (81.6%)	4192 (80.3%)	7321 (82.3%)	0.694
Intravenous thrombolysis (ischaemic)	1339 (12.3%)	368 (8.8%)	1031 (14.4%)	**0.018**
Intravenous thrombolysis (ischaemic)| |	1339 (28.3%)	368 (20.4%)	1031 (32.8%)	0.181
Discharged on antihypertensives#	8763 (70.6%)	3189 (69.5%)	5574 (71.2%)	0.452
Care plan on discharge to community**	3196 (52.3%)	1008 (45.2%)	2188 (56.4%)	0.185

*compared the difference between Queensland and non-Queensland patients

† missing data <2%; ‡ missing data 6-8%; § missing data 22%; | | among those aged ≤85 with admission time ≤3.5 hours; # among those discharged; ** among those discharged to community

Appendix F: Sex difference in specific-cause mortality and excess death rates after stroke: the Australian Stroke Clinical Registry

Supplemental Table F-1. Primary causes of death up to 1 year after stroke in AuSCR 2010-2013 (n=9,441) by sex

Cause of death (COD) †	Men (967 deaths)		Women (1113 deaths)		p-value
	n	%	N	%	
Stroke	398	41.2*	560	50.3*	**0.016**
Ischaemic stroke	87	21.9	114	20.4	
Intracerebral haemorrhagic stroke	123	30.9	168	30.0	
Subarachnoid haemorrhage	10	2.5	15	2.7	
Undetermined	178	3.5	263	6.0	
Ischaemic heart diseases (IHD)	81	8.4*	62	5.6*	**0.016**
Acute myocardial infarction	33	40.7	31	50.0	
Other acute ischaemic heart diseases	3	3.7	0	0	
Chronic ischaemic heart disease	45	55.6	31	50.0	
Other cardiovascular diseases (CVD)	129	13.3*	181	16.3*	0.083
Hypertensive diseases	5	3.9	6	3.3	
Atrial fibrillation	58	45.0	89	49.2	
Heart failure	4	3.1	10	5.5	
Peripheral vascular diseases	9	7.0	9	5.0	
Other cerebrovascular diseases (not stroke)	30	23.3	42	23.2	
Other diseases	23	17.8	25	13.8	
Cancer	120	12.4*	70	6.3*	**<0.001**
Lung	14	11.7	13	18.6	
Brain	12	10.0	6	8.6	
Digestive system	31	25.8	23	32.9	
Breast	0	0	2	2.9	
Female genital organs	-	-	4	5.7	
Male genital organs	15	12.5	-	-	
Skin	11	9.2	4	5.7	
Unknown site	10	8.3	3	4.3	
Lymphoid, hematopoietic and related tissue	15	12.5	10	14.3	
Urinary tract	9	7.5	2	2.9	
Other causes	3	2.5	3	4.3	
Other conditions	141	14.6*	147	13.2*	0.434
Digestive system	16	11.4	23	15.7	
Respiratory system	10	7.1	13	8.8	
Skin and subcutaneous tissue	1	0.7	2	1.4	
Musculoskeletal system	4	2.8	2	1.4	
Genitourinary system	9	6.4	9	6.1	
Congenital malformations	2	1.4	1	0.7	
Infection	6	4.3	7	4.8	
Unclassified conditions	73	51.8	74	50.3	
Accidents	20	14.1	16	10.9	
Unknown (missing on COD)	98	10.1*	93	8.4*	0.218

*Percentages of six major groups of COD (stroke, IHD, CVD, cancer, other conditions and unknown cause) add up to 100%; the subcategories, if available, under each major group also add up to 100%; † Sourced from the National death index (Australian Institute of Health and Welfare)

Supplemental Table F-2. Specific hazard ratio (sHR) of death up to 1 year for those with more severe stroke* compared to those with less severe stroke men in AuSCR 2010-2013 (n=9,441)

Cause of death (COD)	sHR	(95% CI)
Stroke	**8.50**	**(6.14-11.76)**
Ischaemic heart diseases	**2.24**	**(1.58-3.19)**
Other cardiovascular diseases	**4.90**	**(3.71-6.46)**
Cancer	1.04	(0.78-1.38)
Other conditions	**2.99**	**(2.00-4.46)**
Unknown (missing on COD)	**2.30**	**(1.48-3.57)**

Bold denotes statistically significant results

*more severe stroke was defined as unable to walk without assistance on admission

Supplemental Table F-3. Specific hazard ratio (sHR) of death up to 1 year after stroke for women compared to men in AuSCR 2010-2013 using competing risk models by time to death

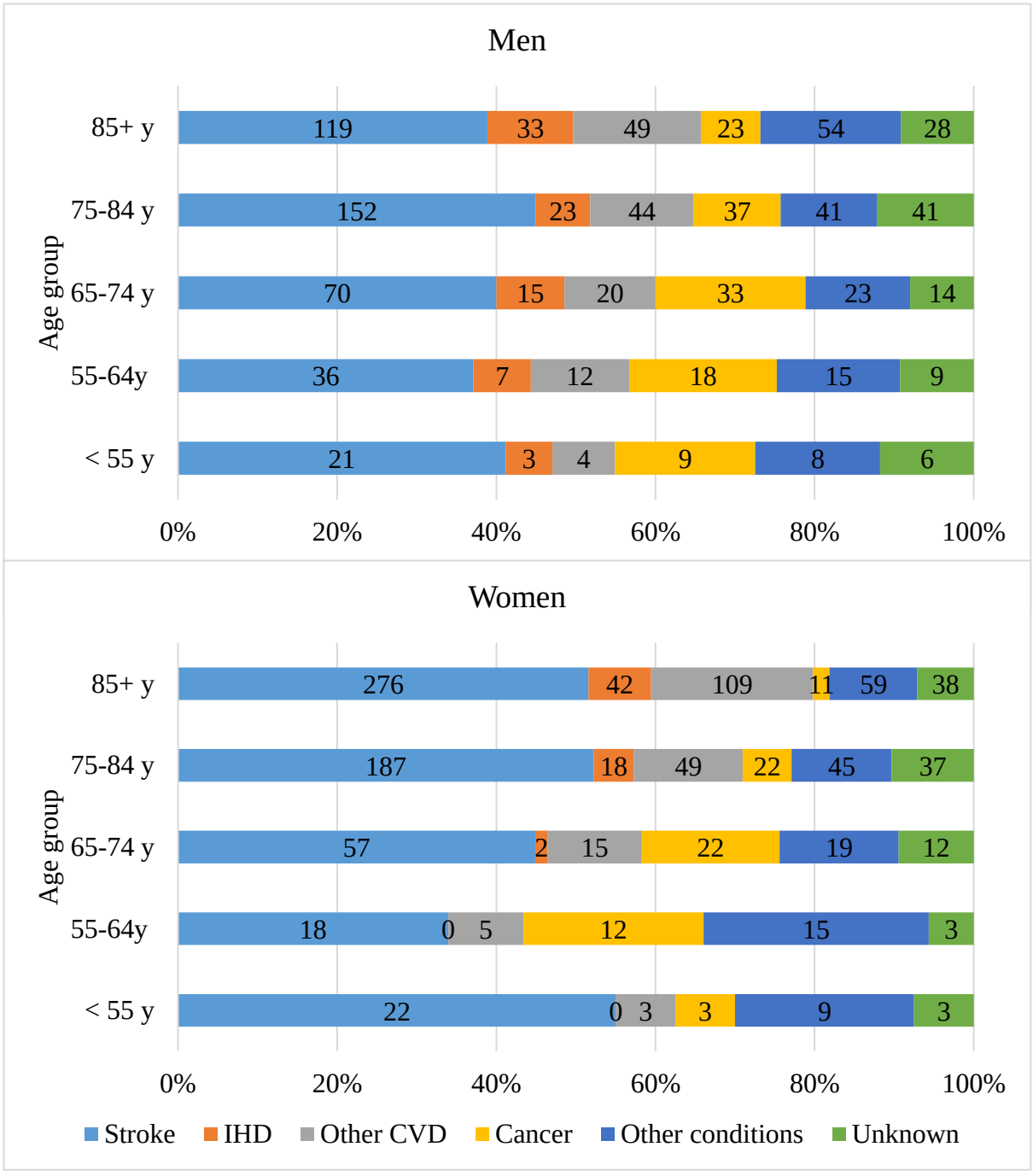
Cause of death	**Unadjusted**		**Adjusted for**			
			Age		Stroke severity†		Age and severity	
	sHR (95% CI)		sHR (95% CI)		sHR (95% CI)		sHR (95% CI)	
Stroke	**1.65**	**(1.42-1.91)**	**1.28**	**(1.10-1.49)**	**1.46**	**(1.25-1.71)**	**1.19**	**(1.02-1.40)**
≤1m (n=8889)	**1.56**	**(1.33-1.83)**	**1.26**	**(1.07-1.49)**	**1.38**	**(1.17-1.63)**	**1.18**	**(1.01-1.39)**
>1–3ms (n=7637)	**2.05**	**(1.40-3.00)**	1.40	(0.99-1.99)	**1.85**	**(1.25-2.72)**	1.30	(0.91-1.87)
>3–6ms (n=7324)	**1.78**	**(1.22-2.59)**	1.14	(0.73-1.76)	**1.64**	**(1.13-2.38)**	1.05	(0.68-1.62)
>6–12ms (n=7098)	**2.23**	**(1.32-3.79)**	1.43	(0.88-2.35)	**2.04**	**(1.18-3.54)**	1.36	(0.81-2.27)
Ischaemic heart disease	0.88	(0.65-1.18)	**0.60**	**(0.45-0.79)**	0.82	(0.60-1.12)	**0.58**	**(0.43-0.77)**
≤1m (n=8889)	1.01	(0.68-1.51)	**0.69**	**(0.49-0.97)**	0.91	(0.61-1.38)	**0.66**	**(0.47-0.92)**
>1–3ms (n=7637)	0.81	(0.43-1.52)	0.54	(0.29-0.99)	0.81	(0.43-1.52)	0.55	(0.29-1.01)
>3–6ms (n=7324)	0.74	(0.26-2.12)	0.41	(0.14-1.25)	0.69	(0.23-2.03)	0.40	(0.13-1.23)
>6–12ms (n=7098)	0.79	(0.30-2.13)	0.51	(0.19-1.38)	0.76	(0.29-2.00)	0.50	(0.19-1.34)
Other cardiovascular disease	**1.65**	**(1.29-2.12)**	1.19	(0.91-1.56)	**1.49**	**(1.16-1.93)**	1.12	(0.85-1.48)
≤1m (n=8889)	**1.65**	**(1.22-2.22)**	1.21	(0.89-1.64)	**1.47**	**(1.08-1.99)**	1.12	(0.82-1.55)
>1–3ms (n=7637)	**1.93**	**(1.03-3.62)**	1.28	(0.68-1.42)	**1.78**	**(0.93-3.41)**	1.21	(0.63-2.35)
>3–6ms (n=7324)	1.49	(0.82-2.71)	1.00	(0.51-1.98)	1.37	(0.75-2.49)	0.95	(0.48-1.85)
>6–12ms (n=7098)	1.82	(0.82-4.02)	1.23	(0.51-2.95)	1.71	(0.80-3.66)	1.18	(0.50-2.78)
Cancer	**0.69**	**(0.50-0.95)**	**0.67**	**(0.50-0.91)**	**0.69**	**(0.50-0.94)**	**0.67**	**(0.49-0.91)**
≤1m (n=8889)	0.95	(0.59-1.51)	0.94	(0.62-1.44)	0.88	(0.54-1.42)	0.89	(0.58-1.38)
>1–3ms (n=7637)	1.12	(0.59-2.11)	1.13	(0.60-2.15)	1.08	(0.58-2.04)	1.10	(0.58-2.09)
>3–6ms (n=7324)	**0.46**	**(0.26-0.82)**	**0.40**	**(0.22-0.73)**	**0.48**	**(0.28-0.87)**	**0.42**	**(0.23-0.77)**
>6–12ms (n=7098)	**0.38**	**(0.18-0.78)**	**0.33**	**(0.15-0.74)**	**0.37**	**(0.18-0.76)**	**0.33**	**(0.15-0.72)**
Other conditions	1.17	(0.87-0.58)	0.99	(0.70-1.36)	1.08	(0.79-1.47)	0.94	(0.68-1.30)
≤1m (n=8889)	1.19	(0.85-1.65)	1.04	(0.72-1.50)	1.05	(0.75-1.47)	0.96	(0.67-1.38)
>1–3ms (n=7637)	1.11	(0.60-2.06)	0.84	(0.41-1.72)	1.05	(0.56-1.96)	0.82	(0.40-1.67)
>3–6ms (n=7324)	1.24	(0.70-2.17)	0.95	(0.57-1.60)	1.20	(0.68-2.13)	0.93	(0.55-1.60)
>6–12ms (n=7098)	1.36	(0.82-2.27)	1.08	(0.67-1.74)	1.31	(0.79-2.16)	1.05	(0.66-1.69)
Unknown cause	1.12	(0.84-1.49)	0.89	(0.64-1.21)	1.05	(0.78-1.40)	0.86	(0.63-1.17)
≤1m (n=8889)	1.04	(0.57-1.91)	0.87	(0.45-1.69)	0.91	(0.50-1.70)	0.80	(0.41-1.57)
>1–3ms (n=7637)	1.33	(0.99-1.76)	0.99	(0.73-1.34)	1.26	(0.95-1.69)	0.97	(0.71-1.31)
>3–6ms (n=7324)	**2.32**	**(1.44-3.74)**	**1.74**	**(1.01-2.90)**	**2.19**	**(1.34-3.57)**	1.68	(0.97-2.91)
>6–12ms (n=7098)	0.83	(0.54-1.28)	**0.61**	**(0.39-0.95)**	0.80	(0.52-1.24)	**0.60**	**(0.38-0.93)**

Supplemental Table F-3. Specific hazard ratio (sHR) of death up to 1 year after stroke for women compared to men in AuSCR 2010-2013 using competing risk models by time to death

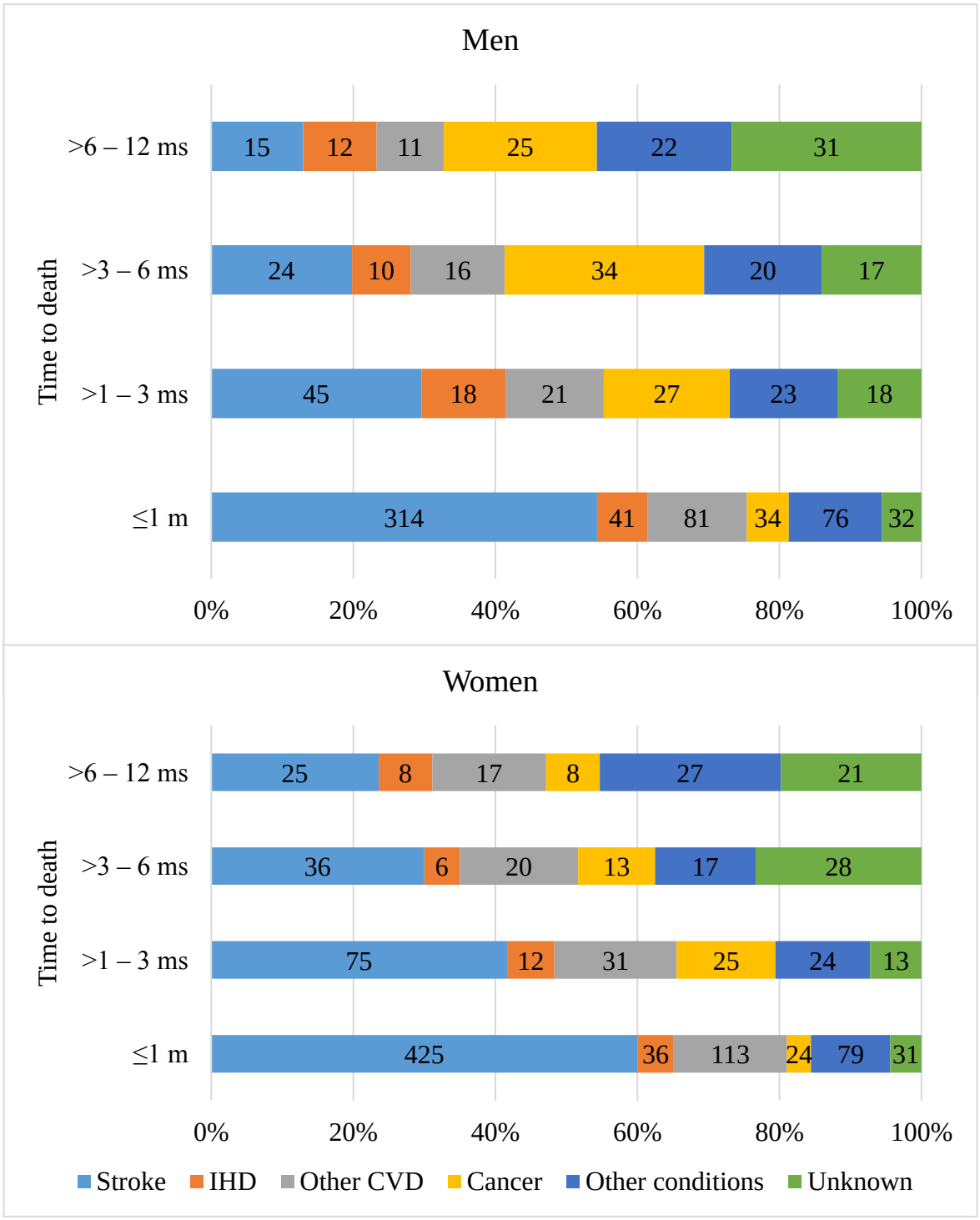
Cause of death	**Unadjusted**	**Adjusted for**		
		Age	Stroke severity†	Age and severity
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)

Bold results denotes statistical significance; m=month

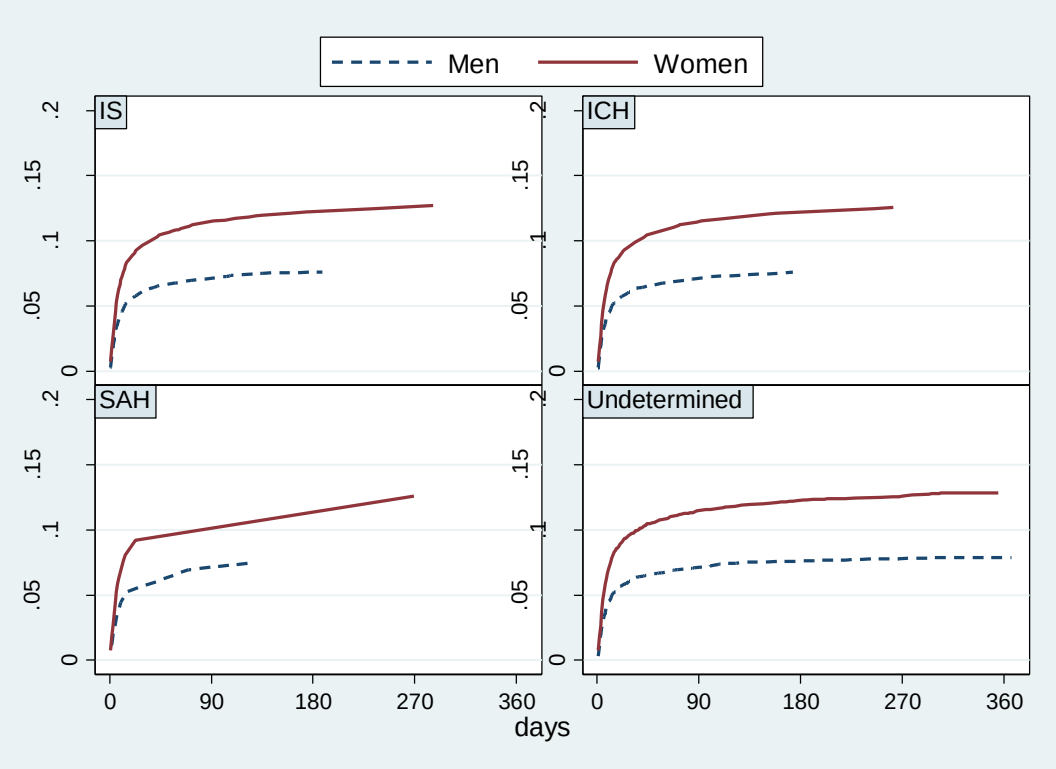
† Walking ability independently on admission was used as a proxy for stroke severity (unable to walk=more severe; able to walk=less severe)



Supplemental Figure F-1. Distribution of causes of death up to 1 year after stroke by sex and age. IHD= Ischaemic heart disease; Other CVD= Other cardiovascular disease (e.g. hypertension, atrial fibrillation); y=year; Unknown=Unknown cause



Supplemental Figure F-2. Distribution of causes of death up to 1 year after stroke by sex and time. IHD= Ischaemic heart disease; Other CVD= Other cardiovascular disease (e.g. hypertension, atrial fibrillation); m=month; Unknown=Unknown cause



Supplemental Figure F-3. Cumulative incidence of death up to 1 year due to stroke by stroke type. IS=Ischaemic stroke; ICH=Intracerebral haemorrhagic stroke; SAH=Subarachnoid haemorrhagic stroke; Undetermined=Undetermined stroke.

Appendix G: Sex differences in health-related quality of life at 3-6 months after stroke: Australian Stroke Clinical Registry

Supplemental Table G-1. Baseline characteristics of stroke survivors assessed and those not assessed with EQ5D at 3-6 months after stroke

	Non-assessed survivors N (%)	Assessed survivors N (%)	P−value
Female, %	2023 (44.4%)	3031 (44.2%)	0.663
Age, median (IQR)	71.4 (59.5, 81.5)	83.0 (75.0, 88.2)	**<0.001**
Age group			
<45	360 (7.8%)	353 (5.2%)	**<0.001**
45-54	452 (9.9%)	527 (7.7%)	
55-64	777 (17.0%)	1065 (15.5%)	
65-74	1068 (23.4%)	1715 (25.0%)	
75-84	1206 (26.5%)	2113 (30.8%)	
85+	697 (15.3%)	1079 (15.8%)	
Stroke−related factors			
Type of stroke			
Haemorrhagic stroke (ICH)	721 (15.8%)	769 (11.2%)	**<0.001**
Ischaemic stroke	3675 (80.5%)	5896 (86.1%)	
Undetermined	168 (3.7%)	186 (2.7%)	
Able to walk at admission (proxy for stroke severity‡)	1692 (39.6%)	2730 (42.5%)	**<0.001**
Evidence−based therapies (%)			
Treated in stroke unit	3656 (80.1%)	6005 (87.6%)	**0.001**
Intravenous thrombolysis*	387 (10.6%)	751 (12.8%)	**0.001**
	387 (30.2%)†	261 (45.2%)†	0.105
Care plan on discharge to community	1113 (51.7%)	1882 (53.7%)	0.103
Discharged on antihypertensives	3037 (67.8%)	5088 (75.0%)	**0.009**
Additional indicators (Queensland data only)			
Mobilisation ≤48 hours if unable to walk on admission	554 (73.5%)	867 (81.1%)	**<0.001**
Aspirin administration ≤ 48 hours*	1014 (68.3%)	1537 (70.1%)	**0.024**
Discharged on antiplatelets or antithrombotic*	1090 (78.9%)	1675 (80.1%)	0.156
Received dysphagia assessment ≤24 hours	902 (51.8%)	1421 (57.0%)	**<0.001**

* among ischaemic strokes; † among those with admission time ≤3.5 hours; ‡ severe = unable to walk independently at admission; not severe = able to walk independently at admission

Supplemental Table G-2. Characteristics, processes of care and discharge information of AuSCR registrants for first−ever stroke during 2010−2014 having EQ5D assessment at 3 months after stroke in Queensland data only

	Assessed (n=2492)			All registrants (n=5224)		
	Men N (%)	Women N (%)	P−value*	Men N (%)	Women N (%)	P−value*
Number of cases	1388 (55.7%)	1104 (44.3%)	**<0.001**	2819 (54.0%)	2405 (46.0%)	**<0.001**
Sociodemographics						
Age, median (IQR)	69.7 (61.1−78.4)	75.4 (63.6−83.7)	**<0.001**	70.9 (61.1−80.1)	77.6 (64.9−85.7)	**<0.001**
Age group						
<45	69 (5.0%)	71 (6.4%)	**<0.001**	153 (5.4%)	143 (6.0%)	**<0.001**
45-54	127 (9.2%)	86 (7.8%)		225 (9.1%)	172 (7.2%)	
55-64	278 (20.0%)	154 (14.0%)		532 (18.9%)	289 (12.0%)	
65-74	424 (30.6%)	230 (20.8%)		777 (27.6%)	433 (18.0%)	
75-84	354 (25.5%)	336 (30.4%)		735 (26.1%)	708 (29.4%)	
85+	136 (9.8%)	227 (20.6%)		366 (13.0%)	660 (27.4%)	
Socioeconomic status						
IRSAD1	316 (22.8%)	253 (22.9%)	0.872	760 (27.0%)	658 (27.4%)	0.994
IRSAD2	281 (20.2%)	215 (19.5%)		557 (18.8%)	476 (19.8%)	
IRSAD3	190 (13.7%)	138 (12.5%)		347 (12.3%)	306 (12.7%)	
IRSAD4	301 (21.7%)	235 (21.3%)		607 (21.5%)	483 (20.1)	
IRSAD5	300 (21.6%)	263 (23.8%)		548 (19.4%)	482 (20.0%)	
Born in Australia	988 (71.2%)	829 (75.1%)	0.277	1925 (68.3%)	1750 (72.8%)	0.075
Aboriginal or Torres Strait Islander	25 (1.8%)	17 (1.6%)	0.924	62 (2.2%)	27 (2.7%)	0.522
Stroke−related factors				546 (19.4%)	383 (15.9%)	**0.010**
Transfer from hospital	264 (19.0%)	186 (16.7%)	0.283			
Stroke while in hospital	64 (4.6%)	69 (6.3%)	0.128	168 (6.0%)	161 (6.7%)	0.394
Time (minutes) from onset to arrival, median (IQR)	190 (83−672)	211 (87−690)	0.261	186 (81−673)	177 (81−553)	0.479
Walking independently at admission (proxy for stroke severity‡)	579 (42.0%)	373 (33.8%)	**0.002**	992 (35.2%)	653 (27.2%)	**<0.001**
Cause of stroke known	705 (50.8%)	518 (47.0%)	**<0.001**	1390 (49.3%)	1104 (45.9%)	0.055
Type of stroke						
Intracerebral haemorrhagic (ICH)	165 (11.9%)	135 (12.2%)	0.541	2302 (81.7%)	1930 (80.3%)	0.415
Ischaemic stroke	1190 (85.7%)	932 (84.4%)		441 (15.6%)	387 (16.1%)	
Undetermined	33 (2.4%)	37 (3.4%)		76 (2.7%)	88 (3.7%)	
Discharge information						
Length of stay if discharged, median (IQR)	5 (3−9)	6 (3−10)	**<0.001**	5 (3−9)	6 (3−11)	**0.001**

Supplemental Table G-2. Characteristics, processes of care and discharge information of AuSCR registrants for first−ever stroke during 2010−2014 having EQ5D assessment at 3 months after stroke in Queensland data only

	Assessed (n=2492)			All registrants (n=5224)		
	Men N (%)	Women N (%)	P−value*	Men N (%)	Women N (%)	P−value*
Discharge destination						
Died in hospital	–	–		246 (8.7%)	254 (10.6%)	**<0.001**
Aged care	24 (1.7%)	61 (5.5%)	**<0.001**	75 (2.7%)	158 (6.6%)	
Home	716 (51.6%)	496 (44.9%)		1171 (41.5%)	827 (34.4%)	
Rehabilitation	391 (28.2%)	320 (29.0%)		708 (25.1%)	566 (23.5%)	
Hospitals/other	257 (18.5%)	227 (20.6%)		619 (22.0%)	600 (25.0%)	
Evidence−based therapies						
Treated in stroke unit	1229 (88.5%)	948 (85.9%)	0.507	2312 (82.0%)	1880 (78.2%)	0.215
Intravenous thrombolysis*	122 (10.4%)	89 (9.7%)	0.730	767 (12.5%)	632 (12.1%)	0.458
	122 (25.9%)†	89 (28.7%)†	0.400	767 (33.1%)†	632 (36.1%)†	0.175
Discharged on antihypertensives	1003 (73.6%)	769 (70.6%)	0.348	1776 (70.8%)	1413 (68.0%)	0.114
Care plan on discharge to community	339 (45.8%)	240 (43.1%)	0.372	578 (46.4%)	430 (43.7%)	0.582

IRSAD; Index of Relative Socioeconomic Advantage and Disadvantage

* among ischaemic strokes

† among those with admission time ≤3.5 hours

‡ severe = unable to walk independently at admission; not severe = able to walk independently at admission

Supplemental Table G-3a. Difference in EQ5D domain scores (1-3) between women and men at 3-6 months after stroke, among those were assessed (n=6852)

	Men (n=3821)		Women (n=3031)		P value
Dimension	n	%	n	%	
Mobility					
1 (no problem)	1752	45.9%	1402	46.3%	0.264
2	1888	49.4%	1369	45.2%	
3 (severe problem)	181	4.7%	260	8.6%	
Self-care					
1	2739	71.7%	1905	62.9%	**<0.001**
2	786	20.6%	711	23.5%	
3	296	7.8%	415	13.7%	
Usual activity					
1	1721	45.0%	1085	35.8%	**<0.001**
2	1453	38.0%	1283	42.3%	
3	647	16.9%	663	21.9%	
Pain/discomfort					
1	2058	53.9%	1410	46.5%	**0.002**
2	1603	42.0%	1432	47.3%	
3	160	4.2%	189	6.2%	
Anxiety/depression					
1	2152	56.3%	1475	48.7%	**0.007**
2	1460	38.2%	1377	45.4%	
3	209	5.5%	179	5.9%	

Supplemental Table G-3b. Relative risk (RR) of having any problem in each dimension of EQ5D for women compared to men, using log-binomial regression

Any problem in	Age (years)	Unadjusted		Adjusted for stroke severity*	
		RR	95% CI	RR	95% CI
Mobility	<65	1.02	0.90, 1.16	1.02	0.90, 1.16
	65-74	0.96	0.83, 1.10	0.96	0.84, 1.11
	>75	1.02	0.92, 1.12	1.02	0.92, 1.12
Self-care	<65	0.81	0.65, 1.01	0.80	0.64, 1.00
	65-74	1.08	0.88, 1.31	1.02	0.84, 1.24
	>75	**1.32**	**1.18, 1.47**	**1.25**	**1.12, 1.40**
Usual activity	<65	0.94	0.82, 1.08	0.93	0.82, 1.07
	65-74	**1.16**	**1.01, 1.33**	1.13	0.98, 1.30
	>75	**1.18**	**1.08, 1.29**	**1.16**	**1.06, 1.26**
Pain/discomfort	<65	0.90	0.77, 1.04	0.89	0.77, 1.03
	65-74	1.10	0.95, 1.28	1.08	0.93, 1.25
	>75	**1.20**	**1.09, 1.33**	**1.18**	**1.08, 1.31**
Anxiety/depression	<65	1.02	0.89, 1.17	1.02	0.89, 1.16
	65-74	**1.29**	**1.11, 1.52**	**1.27**	**1.09, 1.49**
	>75	**1.19**	**1.09, 1.33**	**1.18**	**1.06, 1.30**

*more severe stroke was defined as unable to walk without assistance on admission

Supplemental Table G-4. Sensitivity analyses accounting for missing data of EQ5D data among survivors at 3-6 months after stroke

	Complete−case analysis				**Inverse probability weighting (IPW)**		**Multiple imputation (MI)**				**MI combined with IPW**	
Age (years)	Unable to walk* n	MD (95% CI)	Able to walk* n	MD (95% CI)	Unable to walk MD (95% CI)	Able to walk MD (95% CI)	Unable to walk n	MD (95% CI)	Able to walk n	MD (95% CI)	Unable to walk MD (95% CI)	Able to walk MD (95% CI)
<65	889	0 (-0.035, 0.035)	993	0.010 (-0.024, 0.043)	0.004 (-0.023, 0.030)	0.010 (-0.022, 0.042)	1698	-0.005 (-0.024, 0.015)	1601	0.004 (-0.020, 0.028)	-0.005 (-0.296, 0.021)	0.004 (-0.027, 0.035)
65-74	856	-0.018 (-0.053, 0.017)	743	**-0.087 (-0.131, -0.043)**	-0.013 (-0.042, 0.016)	**-0.087 (-0.121, -0.053)**	1439	-0.008 (-0.024, 0.007)	1161	**-0.069 (-0.134, -0.004)**	-0.008 (-0.036, 0.020)	-0.061 (-0.130, 0.008)
>75	1951	**-0.103 (-0.160, -0.047)**	1054	-0.034 (-0.072, 0.003)	**-0.103 (-0.129, -0.077)**	**-0.031 (-0.053, -0.008)**	3139	**-0.101 (-0.113, -0.088)**	1656	**-0.031 (-0.060, -0.003)**	**-0.101 (-0.126, -0.076)**	**-0.028 (-0.051, -0.006)**

MD = median difference in EQ5D scores for women compared to men; CI = confidence interval

* unable to walk independently at admission = more severe stroke; able to walk independently at admission = less severe stroke

Supplemental Table G-5. Net mean difference in EQ5D utility scores between AuSCR stroke survivors and the general population norms

	Population norms*						AuSCR utility EQ5D scores (DCE)†						Net difference between normal norms and AuSCR		
	Male			Female			Male			Female			Male	Female	Female vs Male
Age	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	n	Mean utility	SD	MD (95% CI)	MD (95% CI)	Net difference
< 55	948	0.93†	0.12†	944	0.88	0.12	520	0.70	0.27	360	0.73	0.24	0.23 (0.21, 0.25)	0.15 (0.12, 0.18)	-0.08
55−64	217	0.90	0.14	226	0.88	0.15	709	0.68	0.28	356	0.69	0.28	0.22 (0.19, 0.25)	0.19 (0.16, 0.23)	-0.03
65−74	153	0.87	0.16	193	0.87	0.16	1098	0.71	0.29	617	0.66	0.33	0.16 (0.13, 0.19)	0.21 (0.18, 0.24)	0.05
75+	104	0.85	0.16	122	0.82	0.15	1494	0.64	0.34	1698	0.53	0.38	0.21 (0.18, 0.25)	0.27 (0.24, 0.30)	0.06
Total	1422			1483			3821				3031				

MD (95% CI), mean difference (95% Confidence Interval)

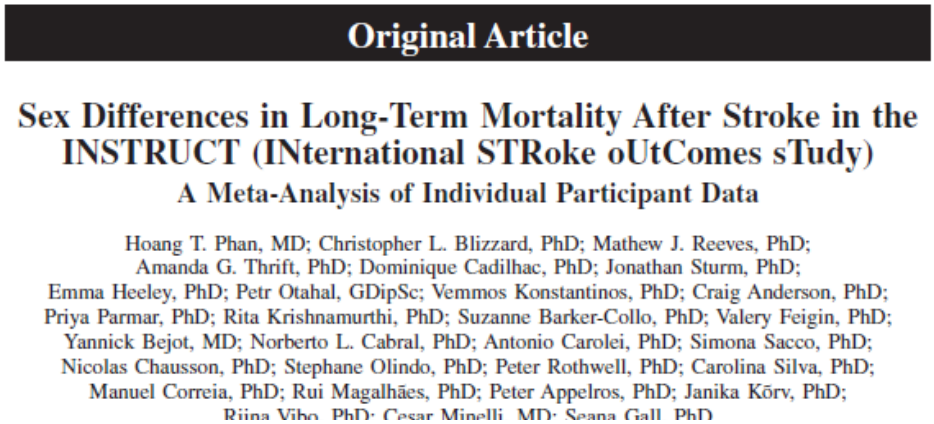
* from McCaffrey et al (2016); the score for group <55 was used by weighted estimates from age 15−54

Supplemental Table G-6. EQ5D utility scores among people with stroke in different populations

Study	Year	Stroke survivors		People without stroke	
		Mean	**SD**	**Mean**	**SD**
AuSCR registry, (3-6 months; current study)	2009-2014	0.64	0.33	0.83*	0.16
Oxford study, UK (6 months)[456]	2002-2007	0.70	0.29	0.85	0.23
AVAIL study, US (3 months; ischaemic only)[110]	2006-2008	Median 0.83	IQR 0.76-1	-	-
Vietnam (3 months)[457]	2012	0.67	0.30	0.91†	0.15
KOSCO study, Korea (6 months)[117]	2012-2014	0.82	0.19	0.95‡	0.001

IQR: Interquartile range
* from McCaffrey et al (2016)[374]
† from Nguyen et al (2017)[458]
‡ from Kwon et al (2018)[459]

Appendix H: Publication 1



Original Article

Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy)

A Meta-Analysis of Individual Participant Data

Hoang T. Phan, MD; Christopher L. Blizzard, PhD; Mathew J. Reeves, PhD; Amanda G. Thrift, PhD; Dominique Cadilhac, PhD; Jonathan Sturm, PhD; Emma Heeley, PhD; Petr Otahal, GDipSc; Vemmos Konstantinos, PhD; Craig Anderson, PhD; Priya Parmar, PhD; Rita Krishnamurthi, PhD; Suzanne Barker-Collo, PhD; Valery Feigin, PhD; Yannick Bejot, MD; Norberto L. Cabral, PhD; Antonio Carolei, PhD; Simona Sacco, PhD; Nicolas Chausson, PhD; Stephane Olindo, PhD; Peter Rothwell, PhD; Carolina Silva, PhD; Manuel Correia, PhD; Rui Magalhães, PhD; Peter Appelros, PhD; Janika Kõrv, PhD; Riina Vibo, PhD; Cesar Minelli, MD; Seana Gall, PhD

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Appendix I: Publication 2

ARTICLE

Factors contributing to sex differences in functional outcomes and participation after stroke

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Abstract

Objective
To examine factors contributing to the sex differences in functional outcomes and participation restriction after stroke.

Methods
Individual participant data on long-term functional outcome or participation restriction (i.e., handicap) were obtained from 11 stroke incidence studies (1993–2014). Multivariable log-binomial regression was used to estimate the female:male relative risk (RR) of poor functional outcome (modified Rankin Scale score >2 or Barthel Index score <20) at 1 year (10 studies, n = 4,852) and 5 years (7 studies, n = 2,226). Multivariable linear regression was used to compare the mean difference (MD) in participation restriction by use of the London Handicap Scale (range 0–100 with lower scores indicating poorer outcome) for women compared to men at 5 years (2 studies, n = 617). For each outcome, study-specific estimates adjusted for confounding factors (e.g., socio-demographics, stroke-related factors) were combined with the use of random-effects meta-analysis.

Results
In unadjusted analyses, women experienced worse functional outcomes after stroke than men (1 year: pooled $RR_{unadjusted}$ 1.32, 95% confidence interval [CI] 1.18–1.48; 5 years: $RR_{unadjusted}$ 1.31, 95% CI 1.16–1.47). However, this difference was greatly attenuated after adjustment for age, prestroke dependency, and stroke severity (1 year: $RR_{adjusted}$ 1.08, 95% CI 0.97–1.20; 5 years: $RR_{adjusted}$ 1.05, 95% CI 0.94–1.18). Women also had greater participation restriction than men (pooled $MD_{unadjusted}$ −5.55, 95% CI −8.47 to −2.63), but this difference was again attenuated after adjustment for the aforementioned factors ($MD_{adjusted}$ −2.48, 95% CI −4.99 to 0.03).

Conclusions
Worse outcomes after stroke among women were explained mostly by age, stroke severity, and prestroke dependency, suggesting these potential targets to improve the outcomes after stroke in women.

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This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0014861). All of the participating studies had approval from their respective local Ethics Committees.

Glossary

BI = Barthel Index; **CI** = confidence interval; **INSTRUCT** = International Stroke Outcomes Study; **IPD** = individual participant data; **LHS** = London Handicap Scale; **MD** = mean difference; **mRS** = modified Rankin Scale; **RR** = relative risk.

It is not often recognized that the burden of stroke falls more heavily on women than men.[1] Women appear to experience worse functional outcomes than men after stroke, meaning they are more often restricted in activities of daily living[2] and are more likely to require supported care.[3] There is also evidence that women experience greater participation restriction (or handicap)—reflecting the influence of functional loss on a person's social, economic, and recreational activities—compared to men after stroke.[4] Participation restriction is rarely measured in stroke outcomes research, although it is a person-centered outcome that is important to survivors of stroke[5] and can greatly affect stroke survivor's health-related quality of life.[6]

It is important not only to document sex differences in functional outcomes and participation restriction but also to understand what accounts for these differences to inform interventions to address these disparities.[7] The causes of differences between women and men in these outcomes have not been conclusively determined in either short- or long-term studies after stroke,[4,8] partly because there have been few well-conducted studies designed to examine the etiology of sex differences in stroke outcomes. Many studies have been based on hospital or convenience samples for which selection bias may adversely affect conclusions. Existing research has often reported the associations between sex and outcomes as incidental findings in multivariable models (e.g., using stepwise regression) with considerable variation in outcome measurement and adjustment for covariates.

We established our collaboration to examine sex differences in stroke outcomes from pooled data obtained from only high-quality population-based studies with long-term follow-up of outcomes.[9] Our aims were to quantify the sex differences in functional outcome and participation restriction in the long term after stroke and to identify the factors that contribute to these disparities.

Methods

The International Stroke Outcomes Study (INSTRUCT) is a collaboration of investigators from 13 gold standard population-based stroke incidence studies from Australasia, Europe, South America, and the Caribbean.[9] The 13 included studies in the INSTRUCT represented 59% of the 22 potentially eligible studies later identified by systematic search (appendix e-1, links.lww.com/WNL/A488, figure e-1, links.lww.com/WNL/A489, and table e-1, links.lww.com/WNL/A490). The INSTRUCT, an individual participant data (IPD) meta-analysis of long-term outcomes after stroke, was registered in PROSPERO[10] and performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses IPD guidelines.[11] This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0014861). All of the participating studies had signed informed consent and approval from their respective local ethics committees. Among the 13 studies included in INSTRUCT, 11 had measures of functional outcome or participation restriction collected up to 5 years after stroke.

Outcome measurement

In 9 studies, participants were followed up with face-to-face interviews conducted at 1 and 5 years after stroke, while in 2 studies (Joinville, Tartu), mail or telephone interviews were used (table e-2, links.lww.com/WNL/A490).

Measures of functional outcome included the Barthel Index (BI) and modified Rankin Scale (mRS; table 1). The 20-point version of BI was used in 2 studies (Matão, Melbourne). The mRS, with a score ranging from 0 (no) to 5 (severe disability), was used in the remaining studies. Poor outcome was defined as an mRS score >2[12] or BI score <20.[13]

Two of the cohorts (Melbourne, Auckland) included assessment of participation restriction (see appendix e-2, links.lww.com/WNL/A488, for this terminology) at 5 years after stroke with the London Handicap Scale (LHS).[14] The dimensions of the LHS include orientation, physical independence, mobility, occupation, social interaction, and economic self-efficiency. The overall LHS score, obtained by applying weights to each subdomain score (0 = worst, 6 = no disadvantage), ranges from 0 (very disadvantaged) to 100 (not disadvantaged).[14]

Predictors of outcome

We obtained data on a wide range of factors that might contribute to sex differences based on our previous research.[4] The availability and specification of individual variables differed between studies (appendix e-2, links.lww.com/WNL/A488). We grouped data into the following categories: (1) sociodemographics (n = 5 variables), (2) prestroke health (dependence, comorbidities, health behaviors; n = 14 variables), (3) stroke-related factors (stroke type, stroke severity, year of stroke occurrence), (4) treatment and management (n = 14 variables), and (5) poststroke factors (poststroke depression, stroke recurrence up to 5 years of follow-up). In general, these factors were from interviews conducted within a few days of the index event with patients and families, medical records, and/or physician consultation.

Statistical analysis

All data were analyzed with Stata 12.1 (StataCorp, College Station, TX). All 2-tailed values of $p \leq 0.05$ were considered statistically significant.

Table 1 Details of included cohorts, baseline with first-ever strokes, and long-term functional outcome and participation after stroke

				1-y Outcome			5-y Outcome		
Study	ID	Study year	Baseline, n	Survivor, n	Assessed, n	Instrument	Survivors, n	Assessed, n	Instrument
Oxford, UK	A	2002–2013	1,374	988	910	mRS	403[a]	385	mRS
Joinville, Brazil	B	2009–2014	2,448	1,869	1,708	mRS	598[a]	423	mRS
Melbourne, Australia	C	1996–1999	1,248[b]	806	494	BI	553	460	BI
								351	LHS
Arcadia, Greece	D	1993–1995	555	342	328	mRS	—	—	—
Perth, Australia	E	2000–2001	183	120	36	mRS/BI	—	—	—
Orebro, Sweden	F	1999–2000	377[b]	253	253	mRS/BI	—	—	—
Martinique, French West Indies	H	1998–1999	580	391	391	mRS	265	265	mRS
Porto, Portugal	I	1998–2000	688	484	484	mRS	281 (7 y)[c]	259	mRS
Auckland, New Zealand	K	2002–2003	1,423	993	—	—	881	303	mRS/BI
								266	LHS
Matão, Brazil	M	2003–2004	81	56	54	BI	—	—	—
Tartu, Estonia	N	2002–2003	433[b]	245	194	mRS/BI	161 (4 y)[c]	131	mRS
Total cases			9,390	5,554/7,640 baseline	mRS/BI 4,852	mRS 3,393; BI 2,531	3,142/5,799 baseline	mRS/BI 2,226; LHS 617	mRS 1,766; BI 591; LHS 617

Abbreviations: BI = Barthel Index; ID = identification; LHS = London Handicap Scale; mRS = modified Rankin Scale.
[a] Follow-up data to 5 years were available only among cases with year of stroke from 2002 to 2008 for Oxford (n = 760 at baseline) or with year of stroke from 2009 to 2011 for Joinville (n = 1,020 at baseline).
[b] Not including cases with subarachnoid hemorrhagic stroke at baseline.
[c] Follow-up data on functional outcome were available only at 4 years (for Tartu) or 7 years (for Porto).

A 2-stage analysis method[15] was used to perform random-effects meta-analysis because many covariates were inconsistently measured between studies from different populations. For the first stage, study-specific estimates of unadjusted and adjusted female:male relative risk (RR) of poor functional outcome at 1 year (10 studies) and 5 years (7 studies) after stroke were made with multivariable log-binomial regression. Functional outcomes available at 4 years (Tartu) or 7 years (Porto) were included in 5-year analyses. For analyses of participation restriction, study-specific multivariable linear regression with transformation (appendix e-3, links.lww.com/WNL/A488) was used to compare the mean difference (MD) of LHS total scores (0–100) for women and men (2 studies, Melbourne and Auckland).

Within each study, we assessed the confounding role[16] of covariates in the association between sex and each outcome. Adjustment was done for each variable separately and then for all confounders in multivariable analyses but with age, stroke severity, and prestroke function (where available) forced into a final fully adjusted model (appendix e-3, links.lww.com/WNL/A488). These confounders were further assessed for interaction with sex within each study.

For the second stage of the analysis, unadjusted and adjusted study-specific estimates were pooled in separate meta-analyses, so that the pooled values could be compared to determine the effect of adjustment. Heterogeneity was evaluated with I^2 statistics. Meta-regression was used to account for sources of heterogeneity among study-level characteristics (n = 14 variables, appendix e-3, links.lww.com/WNL/A488).

Three covariates were measured consistently in all studies: year of stroke occurrence, age, and stroke type. To further test the robustness of our findings, we used a single-stage meta-analysis pooling all IPD datasets[17] to examine whether these factors modified the sex effect on poor functional outcome.

Sensitivity analyses

In studies with >20% of data missing on long-term functional outcomes, participation restriction, or covariates, multiple imputation[18] and further sensitivity analyses were performed and

compared with results from complete-case analyses (appendix e-3, links.lww.com/WNL/A488). We performed sensitivity analyses by conducting ordinal modeling of the mRS score, using alternative cut points to define poor outcome with the BI, analyzing subdomain scores of LHS, and (in a subset of studies) including clinical management as covariates (appendix e-3).

Data availability

For purposes of replicating procedures and results, qualified investigators can request access to patient-level data after ethics clearance and approval by all authors.

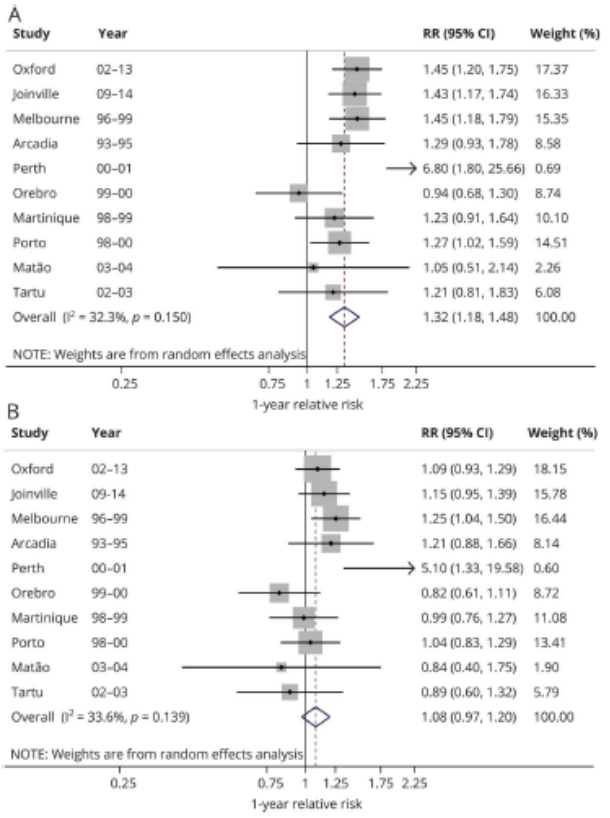
Results

Functional outcomes were assessed among 4,852 (87.3%) of 5,554 survivors at 1 year and 2,226 (70.8%) of 3,142 survivors at 5 years after stroke (table 1). Participation restriction was assessed among 617 (43.0%) of 1,434 survivors at 5 years in 2 of the studies (table 1).

Sex differences in demographics and risk factors

In analyses of baseline factors, among those assessed at 1 year after stroke (table e-3, links.lww.com/WNL/A490), women were older (statistically significant difference in 8 of 10 studies), more often living without a spouse (2 of 3 studies), more often living in institutions (2 of 3 studies), and more often dependent before stroke than men (4 of 6 studies). Men were more frequently ever-smokers (9 of 9 studies) or alcohol consumers (7 of 8 studies) than women. Female survivors at 1 year had more severe strokes than male survivors, with a higher mean score of stroke severity in each study

Figure 1 RR of poor functional outcome at 1 year after stroke for women vs men in (A) unadjusted and (B) adjusted analyses among 10 studies combined using random-effects meta-analysis



Poor outcome was defined as a Barthel Index score <20 (Melbourne and Matão) and modified Rankin Scale score >2 (remaining studies). CI = confidence interval; RR = relative risk.

(significant difference in only 3 of 10 studies). Female survivors at 5 years (table e-4) were older at stroke onset than male survivors (significant difference 3 of 7 studies), and a greater proportion had prestroke dependency (4 of 5 studies).

Sex differences in functional outcomes

Analysis of 1-year functional outcome among 10 studies included 4,657 cases after 4% of available cases were excluded because of missing data on confounders. In unadjusted analyses, women had a 32% greater risk of poor functional outcome than men (figure 1, top). There was no between-study heterogeneity (I^2 = 32.3, p = 0.150). The pooled adjusted RR was 1.08 (95% confidence interval [CI] 0.97–1.20, I^2 = 33.6, p = 0.139; figure 1, bottom). The factors identified as important confounders of the sex differences in functional outcomes included age at baseline (9 of 10 studies), stroke severity (8 of 10 studies), and prestroke dependency (5 of 6 studies; table 2). Only in 2 of 10 studies (Melbourne and Perth) did the poorer functional outcomes for women remain statistically significant after adjustment for these 3 factors (figure 1). There was no evidence that socioeconomic status, cardiovascular risk factors, medical comorbidities, stroke recurrence, and poststroke depression were confounders of the differences (table e-5, links.lww.com/WNL/A490). Adjustment for age alone explained 43% of the sex difference (pooled $RR_{age\text{-}adjusted}$ 1.17, 95% CI 1.06–1.30). The pooled unadjusted female: male RR was also reduced with separate adjustment for stroke severity (20%) and prestroke dependency (45%; table e-6A). Only in the Oxford and Melbourne study, in which the risk of worse functional outcome for women was greater among persons who were independent before stroke (table e-6B), was statistical interaction present. Use of meta-regression did not reveal any sources of heterogeneity (table e-7A). In further analyses of the IPD data, none of the 3 participant-level characteristics of age, stroke type, and year of stroke occurrence were significant sources of between-study variation (table e-7B).

Sensitivity analyses using an alternative cut point for the BI (table e-8, links.lww.com/WNL/A490), ordinal regression model of mRS score (figure e-2, links.lww.com/WNL/A489), and imputation of missing data in 3 studies with substantial missing data (tables e-9 and e-10, A and B) demonstrated that our primary findings were robust (table e-11).

Analyses were repeated for 5-year functional outcomes in 7 studies (n = 2,084, 94% of available cases). Women had a 31% greater risk of poor functional outcome at 5 years (figure 2, top) than men. Adjusted results showed no sex difference (RR 1.05, 95% CI 0.94–1.18; figure 2, bottom) after accounting for age, stroke severity, and prestroke dependency (table 2). Full details of the adjusted analyses (table e-6, A and B, links.lww.com/WNL/A490) and sensitivity analyses are provided in appendix e-4, links.lww.com/WNL/A488, tables e-7B through e-13, and figure e-3, links.lww.com/WNL/A489.

Table 2 Confounding factors contributing to sex difference in long-term functional outcome after stroke based on the fully adjusted model within studies

	1-y		5-y	
Study	**No.**	**Confounders[a]**	**N**	**Confounders[a]**
Oxford	895	Age, log NIHSS,[b] prestroke mRS	378	Age, NIHSS,[c] prestroke mRS, marital status
Joinville	1,708	Age, NIHSS	423	Age,[c] NIHSS[c]
Melbourne	415	Age, log NIHSS,[b] prestroke BI[c]	368	Age, NIHSS, dementia, prestroke BI[c]
Arcadia	327	Age, GCS	—	—
Perth	36	Age, NIHSS,[c] prestroke mRS	—	—
Orebro	253	Age, NIHSS, prestroke Barthel	—	—
Martinique	328	Age, BI at onset	224	Age, BI at onset
Porto	477	Age, LOC,[c] prestroke mRS	258	Age (2-term),[b] LOC,[c] prestroke mRS[2],[b]
Auckland	—	—	302	Age[3], GCS,[c] prestroke dependency[d]
Matão	54	Age, NIHSS	—	—
Tartu	164	Age,[c] NIHSS, prestroke mRS	131	Inverse age[2],[b] NIHSS,[c] prestroke mRS[c]
Total cases	4,657		2,084	

Abbreviations: BI = Barthel Index; GCS = Glasgow Coma Scale; LOC = loss of consciousness; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.
[a] Criteria of being a confounder included the following: (1) the covariate was missing in <20% of cases; (2) the covariate was associated with outcome, $p < 0.1$; (3) the covariate was associated with the exposure, sex, $p < 0.1$; and (4) the inclusion of the covariate in a model with only sex changed the magnitude of the sex coefficient by ≥10%.
[b] Transformations were based on the powers (e.g., second power, 2-power terms, logarithm of covariates) suggested by fractional polynomials because this combination was found to produce the best-fitting multivariable model.
[c] Not meeting criteria of being a confounder but being forced into the fully adjusted multivariable model.
[d] Assessed by whether the patient was living independently before stroke.

Contribution of stroke management to poor functional outcomes based on sex

In a subset of hospitalized patients, there was little evidence of sex differences in the acute treatment and management of stroke among survivors at 1 and 5 years (tables e-14 and e-15, links.lww.com/WNL/A490). None of the factors confounded or modified the association between sex and functional outcomes (figures e-4 and e-5, links.lww.com/WNL/A489).

Sex differences in participation restriction

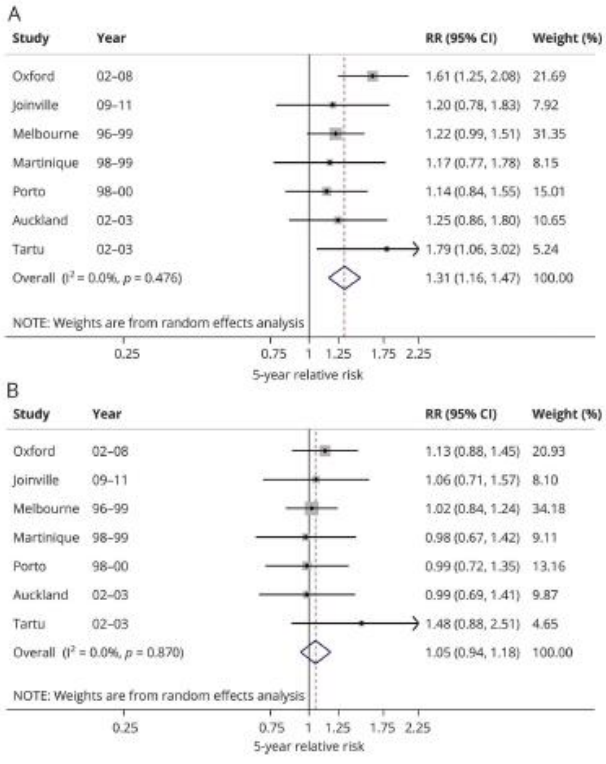
Five years after stroke, data on participation restriction were collected from 351 of 553 (63%) survivors in Melbourne and 266 of 881 (30%) survivors in Auckland (table 1). Men had less participation restriction than women (figure e-6, links.lww.com/WNL/A489).

The pooled unadjusted MD in overall LHS score between women and men was −5.55 (95% CI −8.47 to −2.63). After adjustment for confounders—age, prestroke dependency, prestroke dementia (Melbourne), and stroke severity (Melbourne; table 3)—in study-specific models, the magnitude of the sex difference was attenuated by 55% ($MD_{adjusted}$ −2.48, 95% CI −4.99 to 0.03). There were no significant interactions between sex and these factors in the association with participation restriction. Covariates that did not confound the association are reported in table e-16, links.lww.com/WNL/A490. Further sensitivity analyses suggests that our results were robust (table e-17). In subdimensions of participation (figure e-7, links.lww.com/WNL/A489), women had greater restriction than men in nearly all of the domains (table e-18).

Discussion

Women had worse functional outcomes and greater participation restriction than men in the long term after stroke;

Figure 2 RR of poor functional outcome at 5 years after stroke for women vs men in (A) unadjusted and (B) adjusted analyses among 7 studies combined using random-effects meta-analysis



Poor outcome was defined as a Barthel Index score <20 (Melbourne) or modified Rankin Scale score >2 (remaining studies). CI = confidence interval; RR = relative risk.

Table 3 Sex difference in participation restriction at 5 years among 2 studies (Melbourne and Auckland) with the LHS

	Melbourne (n = 351)		
	MD	95% CI	Δ, %[a]
Unadjusted	−6.89	−10.71 to −3.07	
Adjusted for			
Age[b]	−5.33	−8.78 to −1.87	23
Institutional residence	−6.06	−9.82 to −2.31	12
Prestroke BI[b]	−5.88	−9.69 to −2.07	15
Dementia[b]	−5.79	−9.56 to −2.03	16
NIHSS[b]	−5.61	−9.27 to −1.95	19
Full model[d]	−2.74	−5.95 to 0.47	60
	Auckland (n = 265)		
	MD	95% CI	Δ, %[a]
Unadjusted	−3.89	−8.16 to 0.37	
Adjusted for			
Age[b]	−2.81	−7.00 to 1.38	28
Prestroke dependency[b]	−3.12	−7.25 to 1.01	20
GCS[b,c]	−3.86	−8.12 to 0.41	1
LOC	−3.62	−7.80 to 0.57	7
Full model[d]	−2.05	−6.12 to 2.01	47

Abbreviations: BI = Barthel Index; CI = confidence interval; GCS = Glasgow Coma Scale; LOC = loss of consciousness; LHS = London Handicap Scale; MD = mean difference; NIHSS = NIH Stroke Scale.
[a] Percent change of coefficient of sex difference between unadjusted and adjusted models was calculated by the formula (unadjusted β − adjusted β)/unadjusted β × 100.
[b] Denotes covariates that remained in the final model.
[c] Not meeting criteria of being a confounder but remaining in the fully adjusted multivariable model.
[d] Full models were adjusted for age, prestroke dependency, and severity at baseline; age required quadratic term in the final model (age^2).

however, these differences were greatly diminished after adjustment for major confounding factors.

Age was one of the most important factors contributing to the sex differences in the outcomes examined (43% to functional outcomes, 25% to participation restriction). The elderly often present with more severe strokes and comorbidities,[19] which are associated with poorer recovery after stroke. Older people are also less often admitted to hospital and may not receive a full diagnostic workup or care in a stroke unit,[20] thereby contributing to their worse functional outcomes. One interpretation of older age at stroke onset in women is the success of preventive efforts because they live stroke free for longer, but as a consequence, they are then frailer and have less capacity to recover after stroke compared to men.

More severe strokes in women often contributed to the sex difference in functional outcome and participation restriction. In each study, the mean stroke severity score was consistently higher in women but only significantly different in 3 studies. Factors known to be modifiable contributors to stroke severity include hypertension,[21] hyperlipidemia,[21] and atrial fibrillation,[22] but their relative importance to severity in women compared to men is unknown.

Worse prestroke function in women was another important confounder of the sex differences in the outcomes. Having existing functional limitations may affect discharge destination, particularly the choice of rehabilitation setting.[23] This can greatly affect subsequent rehabilitation outcomes, especially functional recovery, in women after stroke.[24] The presence of prestroke functional limitation may also contribute to participation restriction after stroke through reduced autonomy and social interactions.[25]

The sex difference in outcomes after stroke disappeared after accounting for age, stroke severity, and prestroke function. However, in 2 of 10 studies, the poorer functional outcome in women was not fully explained by these 3 factors. There might be other biological, social, or psychological differences between men and women accounting for differences in

outcomes. One possibility is that women's greater musculoskeletal pain and fear of falling[26] could be barriers to engaging in effective rehabilitation, which could affect their functional recovery and participation restriction after stroke. Another possible explanation is sex differences in perceived physical ability.[27] For example, women generally report greater fear of injury and risk taking compared to men.[28] They may therefore perform fewer activities such as stair climbing even though they are physically capable. This may translate to worse scores on measures of functional ability for women. Because of women's greater social isolation, more social supports may be needed to reduce sex differences in long-term outcomes of stroke.[29]

On the basis of these findings, we can suggest some strategies to address the sex differences in outcomes after stroke. Given the overwhelming role of age on outcomes, the development of evidence-based recommendations applicable to older patients for healthy aging, stroke prevention, and clinical management of cardiovascular diseases is of utmost importance.[30] Although poorer outcomes after stroke in the elderly are to some degree inevitable because of functional deterioration and multimorbidity, we may be able to moderate the impact of stroke by providing evidence for acute stroke care in older people with frailty because such people are often excluded from trials.[30]

Better rehabilitation of those with prestroke functional limitations may assist women with stroke to recover their function and increase participation. Some allied health interventions such as strength and aerobic exercise and support services appear to increase participation,[31] but these programs are not widely available. Consequently, there is a need to implement effective community-based poststroke rehabilitation,[25] especially targeting those who have less capacity to recover. More generally, efforts to help older women maintain their physical function in the general population should be a priority.

Further examination of the causes of the sex difference in stroke severity may identify novel targets to lessen the severity and improve outcomes in women. These differences may be biological or clinical and therefore amenable to intervention. However, they could also be an artifact of measurement, with others reporting that severity assessments are affected by frailty and comorbidities, which are more common in women.[32] In general, it may be necessary to re-evaluate all stroke assessment scales in terms of their suitability across different patient groups, including women, to ensure that they are robust measures of the patient experience.[33] Until we better understand the sex difference in stroke severity, we should optimize control of the risk factors that are associated with severity and poor outcome of stroke, especially in women.[34]

Participation restriction is an important patient-centered outcome after stroke, but data are scarce. Current participation instruments (e.g., LHS) were designed to evaluate health care interventions in population rather than individuals,[35] and the assessments may reflect what people do, not what they can do.[36] We therefore examined the sex differences in some but not all dimensions of participation, e.g., communication or household tasks.[37] New instruments to improve the measurement of patient-centered outcomes may address these problems.[5]

This study has several limitations. Three eligible stroke incidence studies that did not participate in INSTRUCT (appendix e-1, links.lww.com/WNL/A488, and table e-1, links.lww.com/WNL/A490) had no sex-specific reports on relevant outcomes to compare our findings. The variation in definitions and measurement of covariates may lead to some bias in the adjusted estimates. Furthermore, there were few data on stroke management and poststroke depression. However, in the studies that included measures of quality of care and depression and in those by other investigators,[38] these factors did not appear to confound the association between sex and functional outcomes. Age, prestroke dependency, and stroke severity were also strongly predictive of mortality after stroke. However, this is unlikely to have influenced our findings because women were also more likely to die after stroke in these data[9] and the current analyses were limited to survivors. Prestroke dependency contributed to the sex difference in functional outcome, but differing measures were used to assess this (mRS, BI, institutional residence). The effect of adjustment was greater in the studies with detailed measures of prestroke function (mRS, BI), suggesting that our adjusted estimates may have residual confounding. The missing data on long-term outcome in some studies (i.e., Melbourne, Perth, Auckland) are potentially a significant methodologic limitation. However, the results of sensitivity analyses using multiple imputation methods (table e-11) suggest that the missing data did not markedly influence our results, but we cannot preclude the possibility of bias.

Several strengths need to be acknowledged. This is an innovative collaborative study in which individual long-term outcome data were obtained from high-quality population-based studies from various countries, making our results generalizable and adequately powered. We examined the role of confounding factors on the sex difference in outcomes using purposeful model building[16] rather than step-wise methods, providing more reliable unadjusted and adjusted pooled estimates compared to the original studies. Sex differences in long-term functional outcomes and participation restriction after stroke were due largely to women's advanced age, more severe stroke, and prestroke functional limitation but not to stroke care. Population-based interventions are needed to decrease sex disparities in these outcomes. Interventions may include reducing the risk factors of stroke particularly in women and the elderly, as well as better measurement and management of functional limitations in women as they age.

Author contributions

Dr. Phan: study concept and design, acquisition, analysis and interpretation of data, literature review, and drafting of the manuscript. Dr. Blizzard, Dr. Reeves, Dr. Thrift, Dr. Cadilhac, Dr. Sturm, Dr. Heeley, and Mr. Otahal: study concept and design, interpretation of data, and critical revision of manuscript for intellectual content. Dr. Vemmos, Dr. Anderson, Dr. Parmar, Dr. Krishnamurthi, Dr. Barker-Collo, Dr. Feigin, Dr. Bejot, Dr. Cabral, Dr. Carolei, Dr. Sacco, Dr. Chausson, Dr. Olindo, Dr. Rothwell, Dr. Silva, Dr. Correia, Dr. Magalhães, Dr. Appelros, Dr. Kõrv, Dr. Vibo, and Dr. Minelli: study concept and design, interpretation of data, and revision of manuscript for intellectual content. Dr. Gall: study concept and design, supervision of the study, acquisition, interpretation of data, and critical revision of manuscript for intellectual content.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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References

1. Lundberg GP, Volgman AS. Burden of stroke in women. Trends Cardiovasc Med 2016;26:81–88.
2. Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. Curr Cardiol Rep 2010;12:6–13.
3. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham Heart Study. Stroke 2009;40:1032–1037.
4. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. Stroke 2012; 43:1982–1987.
5. Salinas J, Sprinkhuizen SM, Ackerson T, et al. An international standard set of patient-centered outcome measures after stroke. Stroke 2016;47:180–186.
6. Sturm JW, Donnan GA, Dewey HM, et al. Quality of life after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke 2004;35:2340–2345.
7. Reeves MJ, Lisabeth LD. The confounding issue of sex and stroke. Neurology 2010; 74:947–948.
8. Appelros P, Hägeras N, Terent A. Case ascertainment in stroke studies: the risk of selection bias. Acta Neurol Scand 2003;107:145–149.
9. Phan HT, Blizzard CL, Reeves MJ, et al. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational STRoke oUtComes sTudy). Circ Cardiovasc Qual Outcomes 2017;10:e003436.
10. Phan H, Blizzard L, Thrift A, et al. Sex Difference in Long-term Outcomes of Stroke in the INternational STroke OUtComes STudy (INSTRUCT): A Meta-analysis of Individual Patient Data: PROSPERO 2016: CRD42016036723. York, UK: Centre for Reviews and Dissemination, University of York; 2016. Available at: crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036723. Accessed September 12, 2016.
11. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA 2015;313:1657–1665.
12. Salter G, Steen C, Keyser JD. Use of the Barthel Index and modified Rankin Scale in acute stroke trials. Stroke 1999;30:1538–1541.
13. Sturm JW, Dewey HM, Donnan GA, Macdonell RAL, McNeil JJ, Thrift AG. Handicap after stroke: how does it relate to disability, perception of recovery, and stroke subtype? The North East Melbourne Stroke Incidence Study (NEMESIS). Stroke 2002; 33:762–768.
14. Harwood RH, Ebrahim S. The London Handicap Scale. J Neurol Neurosurg Psychiatry 2000;69:406.
15. Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. Stat Med 2001;20:2115–2130.
16. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340–349.
17. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. PLoS One 2012;7:e46042.
18. Seaman SR, White IR, Copas AJ, Li L. Combining multiple imputation and inverse-probability weighting. Biometrics 2012;68:129–137.
19. Gur AY, Tanne D, Bornstein NM, et al. Stroke in the very elderly: characteristics and outcome in patients aged >/=85 years with a first-ever ischemic stroke. Neuroepidemiology 2012;39:57–62.
20. Russo T, Felzani G, Marini C. Stroke in the very old: a systematic review of studies on incidence, outcome, and resource use. J Aging Res 2011;2011:108785.
21. Faraji F, Ghasemi K, Talaie-Zanjani A, Mohammadbeigi A. Prognostic factors in acute stroke, regarding to stroke severity by Canadian Neurological Stroke Scale: a hospital-based study. Asian J Neurosurg 2013;8:78–82.
22. Kakar P, Boos CJ, Lip GYH. Management of atrial fibrillation. Vasc Health Risk Manag 2007;3:109–116.
23. Fox J, Garber P, Hoffman M, et al. Morphological characteristics of skeletal muscles in relation to gender. Aging Clin Exp Res 2003;15:264–269.
24. Paolucci S, Bragoni M, Coiro P, et al. Is sex a prognostic factor in stroke rehabilitation? A matched comparison. Stroke 2006;37:2989–2994.
25. Winstein CJ, Stein J, Arena R, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47:e98–e169.
26. Aberg AC. Gender comparisons of function-related dependence, pain and insecurity in geriatric rehabilitation. J Rehabil Med 2005;37:378–384.
27. Roding J, Glader EL, Malm J, Eriksson M, Lindstrom B. Perceived impaired physical and cognitive functions after stroke in men and women between 18 and 55 years of age: a national survey. Disabil Rehabil 2009;31:1092–1099.
28. Harris CR, Jenkins M, Glaser D. Gender differences in risk assessment: why do women take fewer risks than men? Judgment Decis Making 2006;1:48.
29. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol 2008;7:915–926.
30. Rich MW, Chyun DA, Skolnick AH, et al. Knowledge gaps in cardiovascular care of the older adult population: a scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society. Circulation 2016;133:2103–2122.
31. Obembe AO, Eng JJ. Rehabilitation interventions for improving social participation after stroke: a systematic review and meta-analysis. Neurorehabil Neural Repair 2016; 30:384–392.
32. Abdul-Rahim AH, Fulton RL, Sucharew H, et al. National Institutes of Health Stroke Scale item profiles as predictor of patient outcome: external validation on independent trial data. Stroke 2015;46:395–400.
33. Kapoor A, Lanctôt KL, Bayley M, et al. "Good outcome" isn't good enough: cognitive impairment, depressive symptoms, and social restrictions in physically recovered stroke patients. Stroke 2017;48:1688–1690.
34. Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:1545–1588.
35. Harwood RH, Rogers A, Dickinson E, Ebrahim S. Measuring handicap: the London Handicap Scale, a new outcome measure for chronic disease. Qual Health Care 1994; 3:11–16.
36. Hammel J, Magasi S, Heinemann A, Whiteneck G, Bogner J, Rodriguez E. What does participation mean? An insider perspective from people with disabilities. Disabil Rehabil 2008;30:1445–1460.
37. Tse T, Douglas J, Lentin P, Carey L. Measuring participation after stroke: a review of frequently used tools. Arch Phys Med Rehabil 2013;94:177–192.
38. Kim JS, Lee KB, Roh H, Ahn MY, Hwang HW. Gender differences in the functional recovery after acute stroke. J Clin Neurol 2010;6:183–188.

Bibliography

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245-54.

2. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117-71.

3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics—2015 Update: a report from the American Heart Association. Circulation. 2015;131:e29-e322.

4. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015.

5. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Anderson CS. Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989-1990. Stroke. 2002;33:1034-40.

6. Dennis M, O'Rourke S, Lewis S, Sharpe M, Warlow C. Emotional outcomes after stroke: factors associated with poor outcome. Journal of Neurology, Neurosurgery, and Psychiatry. 2000;68:47-52. Available from: PMC

7. Mathers C, Bernard C, Iburg K, Inoue M, Ma Fat D, Shibuya K, et al. Global burden of disease in 2001: data sources, methods and results. Geneva; 2002 [cited 1 September 2007]. Available from: www.who.int/healthinfo/bod/en/index.html

8. Deloitte Access Economics. The economic impact of stroke in Australia. Melbourne, Canberra; 2013.

9. Deloitte Access Economics. Impact of stroke across Australia. Melbourne, Canberra; 2014.

10. Begg S, Barker B, Stevenson C, Stanley L, Lopez A. The burden of disease and injury in Australia 2003. Canberra: AIHW; 2007 [cited 2015 09/08]; PHE 82. Available from: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442459747

11. Gillespie D, Campbell F. Effect of stroke on family carers and family relationships. Nurs Stand. 2011;26:39-46.

12. Feigin VL, Krishnamurthi R, Bhattacharjee R, Parmar P, Theadom A, Hussein T, et al. New Strategy to Reduce the Global Burden of Stroke. Stroke. 2015.

13. Di Carlo A. Human and economic burden of stroke. Age and Ageing. 2009;38:4-5.

14. Feigin VL, Barker-Collo S, McNaughton H, Brown P, Kerse N. Long-term neuropsychological and functional outcomes in stroke survivors: Current evidence and perspectives for new research. International Journal of Stroke [Review]. 2008;3:33-40. Available from: edselc

15. Thrift AG, Cadilhac DA, Thayabaranathan T, Howard G, Howard VJ, Rothwell PM, et al. Global stroke statistics. Int J Stroke. 2014;9:6-18.

16. Mathers CD, Lopez AD, Murray CJ. The burden of disease and mortality by condition: data, methods and results for 2001. Global burden of disease and risk factors. 2006;45:88.

17. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. The Lancet. 2014;383:245-255.

18. Mathers CD, Lopez AD, Murray CJ. Global burden of disease and risk factors [In: The burden of disease and mortality by condition: data, methods, and results for 2001. 2006

19. Paul SL, Srikanth VK, Thrift AG. The large and growing burden of stroke. Curr Drug Targets. 2007;8:786-93.

20. Davidson PM, Mitchell JA, DiGiacomo M, Inglis SC, Newton PJ, Harman J, et al. Cardiovascular disease in women: implications for improving health outcomes. Collegian. 2012;19:5-13.

21. Cadilhac DA, Dewey HM, Vos T, Carter R, Thrift AG. The health loss from ischemic stroke and intracerebral hemorrhage: evidence from the North East Melbourne Stroke Incidence Study (NEMESIS). Health Qual Life Outcomes. 2010;8:49.

22. Australian Institute of Health and Welfare. Stroke and its management in Australia: an update. Canberra: AIHW; 2013 [cited 2015 20 April]; Cat. no. CVD 61. Available from: http://www.aihw.gov.au/

23. Gall S, Phan H, Madsen TE, Reeves M, Rist P, Jimenez M, et al. Focused update of sex differences in patient reported outcome measures after stroke. Stroke [10.1161/STROKEAHA.117.018417]. 2018.

24. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. Stroke. 2012;43:1982-7.

25. Cadilhac DA, Kim J, Lannin NA, Kapral MK, Schwamm LH, Dennis MS, et al. National stroke registries for monitoring and improving the quality of hospital care: A systematic review. Int J Stroke. 2016;11:28-40.

26. Appelros P, Hogeras N, Terent A. Case ascertainment in stroke studies: the risk of selection bias. Acta Neurol Scand. 2003;107:145-9.

27. Bhalla A, Dundas R, Rudd AG, Wolfe CD. Does admission to hospital improve the outcome for stroke patients? Age Ageing. 2001;30:197-203.

28. Roth DL, Haley WE, Clay OJ, Perkins M, Grant JS, Rhodes JD, et al. Race and gender differences in 1-year outcomes for community-dwelling stroke survivors with family caregivers. Stroke. 2011;42:626-31.

29. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. Stroke. 2003;34:2050-9.

30. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovasc Dis. 2003;16 Suppl 1:14-9.

31. Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? Stroke. 1996;27:550-8.

32. Malmgren R, Warlow C, Bamford J, Sandercock P. Geographical and secular trends in stroke incidence. Lancet. 1987;2:1196-200.

33. Liman TG, Heuschmann PU, Endres M, Floel A, Schwab S, Kolominsky-Rabas PL. Changes in cognitive function over 3 years after first-ever stroke and predictors of cognitive impairment and long-term cognitive stability: the Erlangen Stroke Project. Dement Geriatr Cogn Disord. 2011;31:291-9.

34. Di Carlo A, Lamassa M, Wellwood I, Bovis F, Baldereschi M, Nencini P, et al. Stroke unit care in clinical practice: an observational study in the Florence center of the European Registers of Stroke (EROS) Project. Eur J Neurol. 2011;18:686-94.

35. Cabral NL, Muller M, Franco SC, Longo A, Moro C, Nagel V, et al. Three-year survival and recurrence after first-ever stroke: the Joinville stroke registry. BMC Neurol. 2015;15:70.

36. Carolei A, Marini C, Di Napoli M, Di Gianfilippo G, Santalucia P, Baldassarre M, et al. High stroke incidence in the prospective community-based L'Aquila registry (1994-1998). First year's results. Stroke. 1997;28:2500-6.

37. Jonsson AC, Lindgren I, Hallstrom B, Norrving B, Lindgren A. Determinants of quality of life in stroke survivors and their informal caregivers. Stroke. 2005;36:803-8.

38. Jönsson A-C, Delavaran H, Iwarsson S, Ståhl A, Norrving B, Lindgren A. Preventive health: how much does Australia spend and is it enough. Stroke. 2014;45:1784-1790.

39. Chausson N, Olindo S, Cabre P, Saint-Vil M, Smadja D. Five-year outcome of a stroke cohort in Martinique, French West Indies: Part 2. Stroke. 2010;41:594-9.

40. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matao, Brazil: a population-based prospective study. Stroke. 2007;38:2906-11.

41. Ayis SA, Coker B, Rudd AG, Dennis MS, Wolfe CD. Predicting independent survival after stroke: a European study for the development and validation of standardised stroke scales and prediction models of outcome. J Neurol Neurosurg Psychiatry. 2013;84:288-96.

42. Heuschmann PU, Di Carlo A, Bejot Y, Rastenyte D, Ryglewicz D, Sarti C, et al. Incidence of stroke in Europe at the beginning of the 21st century. Stroke. 2009;40:1557-63.

43. Luengo-Fernandez R, Paul NLM, Gray AM, Pendlebury ST, Bull LM, Welch SJV, et al. Population-based study of disability and institutionalization after transient ischemic attack and stroke: 10-year results of the Oxford Vascular Study. Stroke. 2013;44:2854-2861.

44. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year survival after first-ever stroke in the perth community stroke study. Stroke. 2003;34:1842-6.

45. Hardie K, Jamrozik K, Hankey GJ, Broadhurst RJ, Anderson C. Trends in five-year survival and risk of recurrent stroke after first-ever stroke in the Perth Community Stroke Study. Cerebrovasc Dis. 2005;19:179-85.

46. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. Stroke. 2000;31:2080-6.

47. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes : a population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31:1062-8.

48. Wolfe CDA, Crichton SL, Heuschmann PU, McKevitt CJ, Toschke AM, Grieve AP, et al. Estimates of outcomes up to ten years after stroke: analysis from the prospective South London Stroke Register. PLoS Med. 2011;8:e1001033.

49. Patel MD, McKevitt C, Lawrence E, Rudd AG, Wolfe CD. Clinical determinants of long-term quality of life after stroke. Age Ageing. 2007;36:316-22.

50. Czlonkowska A, Ryglewicz D, Weissbein T, Baranska-Gieruszczak M, Hier DB. A prospective community-based study of stroke in Warsaw, Poland. Stroke. 1994;25:547-51.

51. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Takis CE, Grobbee DE, et al. Prognosis of stroke in the south of Greece: 1 year mortality, functional outcome and its determinants: the Arcadia Stroke Registry. J Neurol Neurosurg Psychiatry. 2000;69:595-600.

52. Bejot Y, Catteau A, Caillier M, Rouaud O, Durier J, Marie C, et al. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. Stroke. 2008;39:1945-51.

53. Feigin VL, Barker-Collo S, Parag V, Senior H, Lawes CM, Ratnasabapathy Y, et al. Auckland Stroke Outcomes Study. Part 1: Gender, stroke types, ethnicity, and functional outcomes 5 years poststroke. Neurology. 2010;75:1597-607.

54. Hackett ML, Duncan JR, Anderson CS, Broad JB, Bonita R. Health-related quality of life among long-term survivors of stroke : results from the Auckland Stroke Study, 1991-1992. Stroke. 2000;31:440-7.

55. Giralt D, Domingues-Montanari S, Mendioroz M, Ortega L, Maisterra O, Perea-Gainza M, et al. The gender gap in stroke: a meta-analysis. Acta Neurol Scand. 2012;125:83-90.

56. Zhou G, Nie S, Dai L, Wang X, Fan W. Sex differences in stroke case fatality: a meta-analysis. Acta Neurol Scand. 2013;128:1-8.

57. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8:355-69.

58. Thrift AG, Thayabaranathan T, Howard G, Howard VJ, Rothwell PM, Feigin VL, et al. Global stroke statistics. Int J Stroke. 2017;12:13-32.

59. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. Circulation. 2009;119:107-15.

60. Cadilhac DA, Andrew NE, Lannin NA, Middleton S, Levi CR, Dewey HM, et al. Quality of acute care and long-term quality of life and survival: the Australian Stroke Clinical Registry. Stroke. 2017;48:1026-1032.

61. Glader EL, Stegmayr B, Norrving B, Terent A, Hulter-Asberg K, Wester PO, et al. Sex differences in management and outcome after stroke: a Swedish national perspective. Stroke. 2003;34:1970-5.

62. Corwin LE, Wolf PA, Kannel WB, McNamara PM. Accuracy of death certification of stroke: the Framingham Study. Stroke. 1982;13:818-21.

63. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003;2:43-53.

64. World Health Organization. International classification of impairments, disabilities, and handicaps: a manual of classification relating to the consequences of disease, published in accordance with resolution WHA29. 35 of the Twenty-ninth World Health Assembly, May 1976. 1980.

65. Tate D, Nieuwenhuijsen E. The ICIDH-2: A new classification of disablement. The International Journal of Psychological Rehabilitation. 2002.

66. World Health Organization. International classification of functioning, disability and health: ICF. World Health Organization; 2001.

67. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. Stroke. 2009;40:1032-7.

68. Salinas J, Sprinkhuizen SM, Ackerson T, Bernhardt J, Davie C, George MG, et al. An international standard set of patient-centered outcome measures after stroke. Stroke [10.1161/STROKEAHA.115.010898]. 2016;47:180.

69. Sturm JW, Donnan GA, Dewey HM, Macdonell RA, Gilligan AK, Srikanth V, et al. Quality of life after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2004;35:2340-5.

70. de Graaf JA, van Mierlo ML, Post MWM, Achterberg WP, Kappelle LJ, Visser-Meily JMA. Long-term restrictions in participation in stroke survivors under and over 70 years of age. Disability and Rehabilitation. 2017:1-9.

71. Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. Pharmacoeconomics. 2000;17:13-35.

72. McHorney CA. Health status assessment methods for adults: past accomplishments and future challenges. Annu Rev Public Health. 1999;20:309-35.

73. Moriarty DG, Zack MM, Kobau R. The Centers for Disease Control and Prevention's Healthy Days Measures - population tracking of perceived physical and mental health over time. Health Qual Life Outcomes. 2003;1:37.

74. Golomb BA, Vickrey BG, Hays RD. A review of health-related quality-of-life measures in stroke. Pharmacoeconomics. 2001;19:155-85.

75. Salter KL, Moses MB, Foley NC, Teasell RW. Health-related quality of life after stroke: what are we measuring? Int J Rehabil Res. 2008;31:111-7.

76. Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life-a systematic review. J Clin Epidemiol. 2017;89:188-198.

77. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41:1403-9.

78. Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ-5D index: a critical review. Expert Rev Pharmacoecon Outcomes Res. 2014;14:221-33.

79. Gibson CL. Cerebral ischemic stroke: is gender important? J Cereb Blood Flow Metab. 2013;33:1355-61.

80. Appelros P, Stegmayr B, Terent A. A review on sex differences in stroke treatment and outcome. Acta Neurol Scand. 2010;121:359-69.

81. Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. Curr Cardiol Rep. 2010;12:6-13.

82. Vukovic V, Galinovic I, Lovrencic-Huzjan A, Budisic M, Demarin V. Women and stroke: how much do women and men differ? A review--diagnostics, clinical differences, therapy and outcome. Coll Antropol. 2009;33:977-84.

83. Bushnell CD. Stroke and the female brain. Nat Clin Pract Neurol. 2008;4:22-33.

84. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol. 2008;7:915-26.

85. Tsivgoulis G, Katsanos AH, Caso V. Under-representation of women in stroke randomized controlled trials: inadvertent selection bias leading to suboptimal conclusions. Therapeutic Advances in Neurological Disorders. 2017;10:241-244.

86. Kunst AE, Amiri M, Janssen F. The decline in stroke mortality. Stroke [10.1161/STROKEAHA.110.599712]. 2011;42:2126.

87. Pikija S, Cvetko D, Malojcic B, Trkanjec Z, Pavlicek I, Lukic A, et al. A population-based prospective 24-month study of stroke: incidence and 30-day case-fatality rates of first-ever strokes in Croatia. Neuroepidemiology. 2012;38:164-71.

88. Stranjalis G, Kalamatianos T, Gatzonis S, Loufardaki M, Tzavara C, Sakas DE. The incidence of the first-ever stroke in a Mediterranean island population: the isle of Lesvos stroke study. Neuroepidemiology. 2014;43:206-12.

89. Walker RW, Jusabani A, Aris E, Gray WK, Whiting D, Kabadi G, et al. Post-stroke case fatality within an incident population in rural Tanzania. J Neurol Neurosurg Psychiatry. 2011;82:1001-5.

90. Oh MS, Yu KH, Roh JK, Lee BC. Gender differences in the mortality and outcome of stroke patients in Korea. Cerebrovascular Diseases. 2009;28:427-434.

91. Palnum KD, Andersen G, Ingeman A, Krog BR, Bartels P, Johnsen SP. Sex-related differences in quality of care and short-term mortality among patients with acute stroke in Denmark. Stroke [10.1161/STROKEAHA.108.543819]. 2009;40:1134.

92. Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. Stroke [10.1161/01.STR.31.8.1833]. 2000;31:1833.

93. Andersen MN, Andersen KK, Kammersgaard LP, Olsen TS. Sex differences in stroke survival: 10-year follow-up of the Copenhagen Stroke Study Cohort. Journal of Stroke and Cerebrovascular Diseases. 2005;14:215-220.

94. Gall SL, Donnan G, Dewey HM, Macdonell R, Sturm J, Gilligan A, et al. Sex differences in presentation, severity, and management of stroke in a population-based study. Neurology. 2010;74:975-81.

95. Wang J, Ning X, Yang L, Tu J, Gu H, Zhan C, et al. Sex differences in trends of incidence and mortality of first-ever stroke in rural Tianjin, China, from 1992 to 2012. Stroke. 2014;45:1626-31.

96. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. Stroke. 2003;34:122-6.

97. Vaartjes I, Reitsma JB, Berger-van Sijl M, Bots ML. Gender differences in mortality after hospital admission for stroke. Cerebrovasc Dis. 2009;28:564-71.

98. Wu X, Min L, Cong L, Jia Y, Liu C, Zhao H, et al. Sex differences in health-related quality of life among adult stroke patients in Northeastern China. J Clin Neurosci. 2014;21:957-61.

99. Koton S, Telman G, Kimiagar I, Tanne D. Gender differences in characteristics, management and outcome at discharge and three months after stroke in a national acute stroke registry. Int J Cardiol. 2013;168:4081-4.

100. Yesilot NF, Koyuncu BA, Coban O, Tuncay R, Bahar SZ. Gender differences in acute stroke: Istanbul medical school stroke registry. Neurol India. 2011;59:174-9.

101. Kim JS, Lee KB, Roh H, Ahn MY, Hwang HW. Gender differences in the functional recovery after acute stroke. J Clin Neurol. 2010;6:183-8.

102. Gargano JW, Wehner S, Reeves M. Sex differences in acute stroke care in a statewide stroke registry. Stroke. 2008;39:24-9.

103. Reid JM, Dai D, Gubitz GJ, Kapral MK, Christian C, Phillips SJ. Gender differences in stroke examined in a 10-year cohort of patients admitted to a Canadian teaching hospital. Stroke. 2008;39:1090-5.

104. Gargano JW, Reeves MJ. Sex differences in stroke recovery and stroke-specific quality of life: results from a statewide stroke registry. Stroke. 2007;38:2541-8.

105. Vincent-Onabajo GO, Hamzat TK, Owolabi MO. Are there gender differences in longitudinal patterns of functioning in Nigerian stroke survivors during the first year after stroke? NeuroRehabilitation. 2014;34:297-304.

106. Ghosal MK, Burman P, Singh V, Das S, Paul N, Ray BK, et al. Correlates of functional outcome among stroke survivors in a developing country--a prospective community-based study from India. J Stroke Cerebrovasc Dis. 2014;23:2614-21.

107. Jalayondeja C, Kaewkungwal J, Sullivan PE, Nidhinandana S, Pichaiyongwongdee S, Jareinpituk S. Factors related to community participation by stroke victims six month post-stroke. Southeast Asian J Trop Med Public Health. 2011;42:1005-13.

108. Hommel M, Trabucco-Miguel S, Joray S, Naegele B, Gonnet N, Jaillard A. Social dysfunctioning after mild to moderate first-ever stroke at vocational age. J Neurol Neurosurg Psychiatry. 2009;80:371-5.

109. Lo RS, Cheng JO, Wong EM, Tang WK, Wong LK, Woo J, et al. Handicap and its determinants of change in stroke survivors: one-year follow-up study. Stroke. 2008;39:148-53.

110. Bushnell CD, Reeves MJ, Zhao X, Pan W, Prvu-Bettger J, Zimmer L, et al. Sex differences in quality of life after ischemic stroke. Neurology. 2014;82:922-31.

111. Franzen-Dahlin A, Laska AC. Gender differences in quality of life after stroke and TIA: a cross-sectional survey of out-patients. J Clin Nurs. 2012;21:2386-91.

112. Sheldenkar A, Crichton S, Douiri A, Rudd AG, Wolfe CD, Chen R. Temporal trends in health-related quality of life after stroke: analysis from the South London Stroke Register 1995-2011. Int J Stroke. 2014;9:721-7.

113. Lopez-Espuela F, Zamorano JD, Ramirez-Moreno JM, Jimenez-Caballero PE, Portilla-Cuenca JC, Lavado-Garcia JM, et al. Determinants of Quality of Life in Stroke Survivors After 6 Months, from a Comprehensive Stroke Unit: A Longitudinal Study. Biol Res Nurs. 2014.

114. Zhang X, Sun Q, Wu M, Xia G. Health-related quality of life after stroke: a 2-year prospective cohort study in Wuhan, China. Int J Neurosci. 2013;123:138-41.

115. Czapiga B, Kozba-Gosztyla M, Czapiga A, Jarmundowicz W, Rosinczuk-Tonderys J, Krautwald-Kowalska M. Recovery and quality of life in patients with ruptured cerebral aneurysms. Rehabil Nurs. 2014;39:250-9.

116. Donkor ES, Owolabi MO, Bampoh PO, Amoo PK, Aspelund T, Gudnason V. Profile and health-related quality of life of Ghanaian stroke survivors. Clin Interv Aging. 2014;9:1701-8.

117. Chang WH, Sohn MK, Lee J, Kim DY, Lee SG, Shin YI, et al. Predictors of functional level and quality of life at 6 months after a first-ever stroke: the KOSCO study. J Neurol. 2016;263:1166-77.

118. Chuluunbaatar E, Chou YJ, Pu C. Quality of life of stroke survivors and their informal caregivers: A prospective study. Disabil Health J. 2016;9:306-12.

119. Guajardo VD, Terroni L, Sobreiro Mde F, Zerbini MI, Tinone G, Scaff M, et al. The influence of depressive symptoms on quality of life after stroke: a prospective study. J Stroke Cerebrovasc Dis. 2015;24:201-9.

120. Reeves SL, Brown DL, Baek J, Wing JJ, Morgenstern LB, Lisabeth LD. Ethnic differences in poststroke quality of life in the Brain Attack Surveillance in Corpus Christi (BASIC) Project. Stroke. 2015;46:2896-901.

121. Abubakar SA, Isezuo SA. Health related quality of life of stroke survivors: experience of a stroke unit. Int J Biomed Sci. 2012;8:183-7.

122. Delcourt C, Hackett M, Wu Y, Huang Y, Wang J, Heeley E, et al. Determinants of quality of life after stroke in China: the ChinaQUEST (QUality Evaluation of Stroke care and Treatment) study. Stroke. 2011;42:433-8.

123. Almborg AH, Ulander K, Thulin A, Berg S. Discharged after stroke - important factors for health-related quality of life. J Clin Nurs. 2010;19:2196-206.

124. Shyu YI, Maa SH, Chen ST, Chen MC. Quality of life among older stroke patients in Taiwan during the first year after discharge. J Clin Nurs. 2009;18:2320-8.

125. Lindgren P, Glader EL, Jonsson B. Utility loss and indirect costs after stroke in Sweden. Eur J Cardiovasc Prev Rehabil. 2008;15:230-3.

126. Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. Stroke. 2000;31:1833-7.

127. Santalucia P, Pezzella FR, Sessa M, Monaco S, Torgano G, Anticoli S, et al. Sex differences in clinical presentation, severity and outcome of stroke: results from a hospital-based registry. Eur J Intern Med. 2013;24:167-71.

128. Olsen TS, Andersen ZJ, Andersen KK. Explaining poorer stroke outcomes in women: women surviving 3 months have more severe strokes than men despite a lower 3-month case fatality. Gend Med. 2012;9:147-53.

129. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic review. Stroke. 2009;40:1082-90.

130. Heeley EL, Wei JW, Carter K, Islam MS, Thrift AG, Hankey GJ, et al. Socioeconomic disparities in stroke rates and outcome: pooled analysis of stroke incidence studies in Australia and New Zealand. Med J Aust. 2011;195:10-4.

131. Cox AM, McKevitt C, Rudd AG, Wolfe CD. Socioeconomic status and stroke. Lancet Neurol. 2006;5:181-8.

132. Jakovljević D, Sarti C, Sivenius J, Torppa J, Mähönen M, Immonen-Räihä P, et al. Socioeconomic Status and Ischemic Stroke: The FINMONICA Stroke Register. Stroke. 2001;32:1492-1498.

133. Kapral MK, Wang H, Mamdani M, Tu JV. Effect of socioeconomic status on treatment and mortality after stroke. Stroke. 2002;33:268-275.

134. Preston A, Whitehouse G. Gender differences in occupation of employment within Australia. Perth; 2004.

135. Arrich J, Lalouschek W, Müllner M. Influence of socioeconomic status on mortality after stroke: retrospective cohort study. Stroke. 2005;36:310-314.

136. Kunst AE, del Rios M, Groenhof F, Mackenbach JP, Health ftEUWGoSIi. Socioeconomic inequalities in stroke mortality among middle-aged men: an international overview. Stroke. 1998;29:2285-2291.

137. Samanci N, Dora B, Kizilay F, Balci N, Ozcan E, Arman M. Factors affecting one year mortality and functional outcome after first ever ischemic stroke in the region of Antalya, Turkey (a hospital-based study). Acta Neurol Belg. 2004;104:154-60.

138. Turtzo LC, McCullough LD. Sex Differences in Stroke. Cerebrovascular Diseases (Basel, Switzerland). 2008;26:462-474. Available from: PMC

139. Vogt TM, Mullooly JP, Ernst D, Pope CR, Hollis JF. Social networks as predictors of ischemic heart disease, cancer, stroke and hypertension: incidence, survival and mortality. J Clin Epidemiol. 1992;45:659-66.

140. Wiszniewska M, Niewada M, Czlonkowska A. Sex differences in risk factor distribution, severity, and outcome of ischemic stroke. Acta Clin Croat. 2011;50:21-8.

141. U.S. Census Bureau CHR. American Housing Survey for the United States: 2005. Washington, DC: Office USGP; 2005. Available from: www.census.gov/prod/2006pubs/23-309.pdf

142. Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CD, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. Stroke. 2003;34:1114-9.

143. Lai SM, Duncan PW, Dew P, Keighley J. Sex differences in stroke recovery. Prev Chronic Dis. 2005;2:A13.

144. Arboix A, Oliveres M, Garcia-Eroles L, Maragall C, Massons J, Targa C. Acute cerebrovascular disease in women. Eur Neurol. 2001;45:199-205.

145. Kapral MK, Fang J, Hill MD, Silver F, Richards J, Jaigobin C, et al. Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. Stroke. 2005;36:809-14.

146. Niewada M, Kobayashi A, Sandercock PA, Kaminski B, Czlonkowska A. Influence of gender on baseline features and clinical outcomes among 17,370 patients

with confirmed ischaemic stroke in the international stroke trial. Neuroepidemiology. 2005;24:123-8.

147. Smith DB, Murphy P, Santos P, Phillips M, Wilde M. Gender differences in the Colorado Stroke Registry. Stroke. 2009;40:1078-81.

148. Lasek-Bal A. Profile of risk factors for stroke: sex-and age-related differences. Journal of Health Sciences. 2014;4.

149. Haast RA, Gustafson DR, Kiliaan AJ. Sex differences in stroke. J Cereb Blood Flow Metab. 2012;32:2100-7.

150. Roquer J, Campello AR, Gomis M. Sex differences in first-ever acute stroke. Stroke. 2003;34:1581-5.

151. Forster A, Gass A, Kern R, Wolf ME, Ottomeyer C, Zohsel K, et al. Gender differences in acute ischemic stroke: etiology, stroke patterns and response to thrombolysis. Stroke. 2009;40:2428-32.

152. Kleindorfer DO, Broderick JP, Khoury J, Flaherty ML, Woo D, Alwell K, et al. Emergency department arrival times after acute ischemic stroke during the 1990s. Neurocrit Care. 2007;7:31-5.

153. Nowacki P, Nowik M, Bajer-Czajkowska A, Porebska A, Zywica A, Nocon D, et al. Patients' and bystanders' awareness of stroke and pre-hospital delay after stroke onset: perspectives for thrombolysis in West Pomerania Province, Poland. Eur Neurol. 2007;58:159-65.

154. Faiz KW, Sundseth A, Thommessen B, Ronning OM. Prehospital delay in acute stroke and TIA. Emerg Med J. 2013;30:669-74.

155. Evenson KR, Foraker RE, Morris DL, Rosamond WD. A comprehensive review of prehospital and in-hospital delay times in acute stroke care. Int J Stroke. 2009;4:187-99.

156. Kapral MK, Degani N, Hall R, Fang J, Saposnik G, Richards J, et al. Gender differences in stroke care and outcomes in Ontario. Womens Health Issues. 2011;21:171-6.

157. Foerch C, Misselwitz B, Humpich M, Steinmetz H, Neumann-Haefelin T, Sitzer M. Sex disparity in the access of elderly patients to acute stroke care. Stroke. 2007;38:2123-6.

158. Gargano JW, Wehner S, Reeves MJ. Do presenting symptoms explain sex differences in emergency department delays among patients with acute stroke? Stroke. 2009;40:1114-20.

159. Smith MA, Lisabeth LD, Brown DL, Morgenstern LB. Gender comparisons of diagnostic evaluation for ischemic stroke patients. Neurology. 2005;65:855-8.

160. De Silva DA, Ebinger M, Davis SM. Gender issues in acute stroke thrombolysis. Journal of Clinical Neuroscience. 2009;16:501-504.

161. Lisabeth LD, Brown DL, Morgenstern LB. Barriers to intravenous tissue plasminogen activator for acute stroke therapy in women. Gend Med. 2006;3:270-8.

162. Reeves M, Bhatt A, Jajou P, Brown M, Lisabeth L. Sex differences in the use of intravenous rt-PA thrombolysis treatment for acute ischemic stroke: a meta-analysis. Stroke. 2009;40:1743-9.

163. de Ridder I, Dirks M, Niessen L, Dippel D. Unequal access to treatment with intravenous alteplase for women with acute ischemic stroke. Stroke. 2013;44:2610-2.

164. Sacco RL, Wolf PA, Kannel WB, McNamara PM. Survival and recurrence following stroke. The Framingham study. Stroke. 1982;13:290-5.

165. Ramasubbu R, Patten SB. Effect of depression on stroke morbidity and mortality. Can J Psychiatry. 2003;48:250-7.

166. Zikic TR, Divjak I, Jovicevic M, Semnic M, Slankamenac P, Zarkov M, et al. The effect of post stroke depression on functional outcome and quality of life. Acta Clin Croat. 2014;53:294-301.

167. Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. Stroke. 2006;37:193-8.

168. Poynter B, Shuman M, Diaz-Granados N, Kapral M, Grace SL, Stewart DE. Sex differences in the prevalence of post-stroke depression: a systematic review. Psychosomatics. 2009;50:563-9.

169. Feigin VL, Carter K. Editorial comment—Stroke incidence studies one step closer to the elusive gold standard? Stroke. 2004;35:2045-7.

170. Palm F, Urbanek C, Rose S, Buggle F, Bode B, Hennerici MG, et al. Stroke Incidence and Survival in Ludwigshafen am Rhein, Germany: the Ludwigshafen Stroke Study (LuSSt). Stroke. 2010;41:1865-70.

171. Sienkiewicz-Jarosz H, Gluszkiewicz M, Pniewski J, Niewada M, Czlonkowska A, Wolfe C, et al. Incidence and case fatality rates of first-ever stroke - comparison of data from two prospective population-based studies conducted in Warsaw. Neurol Neurochir Pol. 2011;45:207-12.

172. Elneihoum AM, Göransson M, Falke P, Janzon L. Three-year survival and recurrence after stroke in Malmö, Sweden: an analysis of stroke registry data. Stroke. 1998;29:2114-2117.

173. La Spina P, Savica R, Serra S, Calabro RS, Postorino P, Morgante L, et al. Long-term survival and outcome after first stroke in the Sicilian Aeolian Island Archipelago population. Neurol Sci. 2008;29:153-6.

174. Di Carlo A, Inzitari D, Galati F, Baldereschi M, Giunta V, Grillo G, et al. A prospective community-based study of stroke in Southern Italy: the Vibo Valentia incidence of stroke study (VISS). Methodology, incidence and case fatality at 28 days, 3 and 12 months. Cerebrovasc Dis. 2003;16:410-7.

175. Corso G, Bottacchi E, Giardini G, Di Giovanni M, Meloni T, Pesenti Campagnoni M, et al. Epidemiology of stroke in northern Italy: the Cerebrovascular Aosta Registry, 2004-2008. Neurol Sci. 2013;34:1071-81.

176. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;363:1925-33.

177. Cabral NL, Goncalves AR, Longo AL, Moro CH, Costa G, Amaral CH, et al. Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. J Neurol Neurosurg Psychiatry. 2009;80:755-61.

178. Sturm JW, Donnan GA, Dewey HM, Macdonell RA, Gilligan AK, Thrift AG. Determinants of handicap after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2004;35:715-20.

179. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS, et al. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. Stroke. 1999;30:363-70.

180. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Results from the Perth Community Stroke Study. Stroke. 1994;25:1935-44.

181. Appelros P, Nydevik I, Seiger A, Terent A. High incidence rates of stroke in Orebro, Sweden: Further support for regional incidence differences within Scandinavia. Cerebrovasc Dis. 2002;14:161-8.

182. Smadja D, Cabre P, May F, Fanon JL, Rene-Corail P, Riocreux C, et al. ERMANCIA: Epidemiology of Stroke in Martinique, French West Indies: Part I: methodology, incidence, and 30-day case fatality rate. Stroke. 2001;32:2741-7.

183. Correia M, Silva MR, Matos I, Magalhaes R, Lopes JC, Ferro JM, et al. Prospective community-based study of stroke in Northern Portugal: incidence and case fatality in rural and urban populations. Stroke. 2004;35:2048-53.

184. Feigin V, Carter K, Hackett M, Barber PA, McNaughton H, Dyall L, et al. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002-2003. Lancet Neurol. 2006;5:130-9.

185. Korv J, Roose M, Kaasik A-E. Stroke registry of Tartu, Estonia, from 1991 through 1993. Cerebrovascular Diseases. 1997;7:154-162.

186. Sternbach GL. The Glasgow coma scale. J Emerg Med. 2000;19:67-71.

187. Njemanze PC, Chidi-Ebere A. Three-dimensional vector component analysis of neurological stroke scales. Stroke. 1999;30:1731-1733.

188. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20:864-70.

189. Ali K, Cheek E, Sills S, Crome P, Roffe C. Development of a conversion factor to facilitate comparison of National Institute of Health Stroke Scale scores with Scandinavian Stroke Scale scores. Cerebrovasc Dis. 2007;24:509-15.

190. Snaith RP, Constantopoulos AA, Jardine MY, McGuffin P. A clinical scale for the self-assessment of irritability. Br J Psychiatry. 1978;132:164-71.

191. Paul SL, Dewey HM, Sturm JW, Macdonell RA, Thrift AG. Prevalence of depression and use of antidepressant medication at 5-years poststroke in the North East Melbourne Stroke Incidence Study. Stroke. 2006;37:2854-5.

192. Goldberg D, Williams P. A user's guide to the General Health Questionnaire. Windsor: NFER-Nelson; 1988.

193. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.

194. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199-208.

195. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. Quality of Life Research [journal article]. 1999;8:209-224.

196. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. UK-TIA Study Group. Br Med J (Clin Res Ed). 1988;296:316-20.

197. Moro CH, Goncalves AR, Longo AL, Fonseca PG, Harger R, Gomes DB, et al. Trends of the incidence of ischemic stroke thrombolysis over seven years and one-year outcome: a population-based study in Joinville, Brazil. Cerebrovasc Dis Extra. 2013;3:156-66.

198. Correia M, Magalhães R, Silva MR, Matos I, Silva MC. Stroke types in rural and urban Northern Portugal: incidence and 7-year survival in a community-based study. Cerebrovascular Diseases Extra. 2013;3:137-149.

199. Vibo R, Korv J, Roose M. One-year outcome after first-ever stroke according to stroke subtype, severity, risk factors and pre-stroke treatment. A population-based study from Tartu, Estonia. Eur J Neurol. 2007;14:435-9.

200. Sturm JW, Osborne RH, Dewey HM, Donnan GA, Macdonell RA, Thrift AG. Brief comprehensive quality of life assessment after stroke: the assessment of quality of life instrument in the north East melbourne stroke incidence study (NEMESIS). Stroke. 2002;33:2888-94.

201. Reeves MJ, Lisabeth LD. The confounding issue of sex and stroke. Neurology. 2010;74:947-8.

202. PROSPERO International prospective register of systematic review. York, UK: Centre for Reviews and Dissemination, University of York [cited 2016 12 Sep]. Available from: http://www.crd.york.ac.uk/PROSPERO

203. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. Jama. 2015;313:1657-65.

204. Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. Stat Med. 2001;20:2115-30.

205. Frome EL, Checkoway H. Use of poisson regression models in estimating incidence rates and ratios. American Journal of Epidemiology. 1985;121:309-323.

206. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30:377-99.

207. Greenland S. Modeling and variable selection in epidemiologic analysis. American Journal of Public Health. 1989;79:340-349.

208. Dehlendorff C, Andersen KK, Olsen TS. Sex disparities in stroke: women have more severe strokes but better survival than men. Journal of the American Heart Association. 2015;4.

209. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. International Journal of Epidemiology. 1999;28:964-974.

210. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. PLoS One. 2012;7:e46042.

211. White IR. Multivariate random-effects meta-analysis. Stata Journal. 2009;9:40-56.

212. Sohrabji F, Bake S, Lewis DK. Age-related changes in brain support cells: Implications for stroke severity. Neurochemistry International. 2013;63:291-301.

213. Reeves MJ, Prager M, Fang J, Stamplecoski M, Kapral MK. Impact of living alone on the care and outcomes of patients with acute stroke. Stroke. 2014;45:3083-5.

214. Luker JA, Wall K, Bernhardt J, Edwards I, Grimmer-Somers KA. Patients' age as a determinant of care received following acute stroke: a systematic review. BMC Health Serv Res. 2011;11:161.

215. Yiin GS, Howard DP, Paul NL, Li L, Mehta Z, Rothwell PM. Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. J Neurol Neurosurg Psychiatry. 2015.

216. Fugate JE, Rabinstein AA. Absolute and relative contraindications to iv rt-pa for acute ischemic stroke. Neurohospitalist. 2015;5:110-21.

217. Rich MW, Chyun DA, Skolnick AH, Alexander KP, Forman DE, Kitzman DW, et al. Knowledge gaps in cardiovascular care of the older adult population: a scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society. Circulation. 2016;133:2103-22.

218. Australian Institute of Health and Welfare 2016. Australian Burden of Disease Study: Impact and causes of illness and death in Australia 2011. Australian Burden of Disease Study series no. 3. BOD 4. Canberra: AIHW [cited 2016 15 November]. Available from: http://www.aihw.gov.au/

219. Clow B, Pederson A, Haworth-Brockman M, Bernier J. Rising to the challenge: Sex-and gender-based analysis for health planning, policy and research in Canada. Halifax: Atlantic Centre of Excellence for Women's Health. 2009.

220. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14:392-7.

221. Vlassoff C. Gender differences in determinants and consequences of health and illness. J Health Popul Nutr. 2007;25:47-61.

222. Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. Qjm. 2014;107:955-67.

223. Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. Stroke. 2000;31:822-7.

224. Patel D, Mohanty P, Di Biase L, Sanchez JE, Shaheen MH, Burkhardt JD, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. Heart Rhythm. 2010;7:167-72.

225. Yiin GS, Howard DP, Paul NL, Li L, Luengo-Fernandez R, Bull LM, et al. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. Circulation. 2014;130:1236-44.

226. Hier DB, Yoon WB, Mohr JP, Price TR, Wolf PA. Gender and aphasia in the Stroke Data Bank. Brain Lang. 1994;47:155-67.

227. Di Legge S, Koch G, Diomedi M, Stanzione P, Sallustio F. Stroke prevention: managing modifiable risk factors. Stroke Res Treat. 2012;2012:391538.

228. Minnerup J, Sutherland BA, Buchan AM, Kleinschnitz C. Neuroprotection for stroke: current status and future perspectives. Int J Mol Sci. 2012;13:11753-72.

229. Wang Z, Li J, Wang C, Yao X, Zhao X, Wang Y, et al. Gender differences in 1-year clinical characteristics and outcomes after stroke: results from the China National Stroke Registry. PLoS One. 2013;8:e56459.

230. Bronnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. Stroke. 2001;32:2131-6.

231. Green S, Higgins J. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration; 2011.

232. Hausmann R, Tyson L, Zahidi S. The global gender gap report 2011 2011 [cited 2016 25/02]: Available from: http://www3.weforum.org/docs/WEF_GenderGap_Report_2011.pdf.

233. Bucholz EM, Normand SL, Wang Y, Ma S, Lin H, Krumholz HM. Life expectancy and years of potential life lost after acute myocardial infarction by sex and

race: a cohort-based study of Medicare Beneficiaries. J Am Coll Cardiol. 2015;66:645-55.

234. Group WB. World Development Indicators 2014. Washington, DC: World Bank; 2012 [cited 2014]. Available from: http://data.worldbank.org/indicator

235. Lundberg GP, Volgman AS. Burden of stroke in women. Trends Cardiovasc Med. 2015.

236. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, et al. Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy). A meta-analysis of individual participant data. Circ Cardiovasc Qual Outcomes [10.1161/CIRCOUTCOMES.116.003436]. 2017;10.

237. Phan H, Blizzard L, Thrift A, Cadilhac D, Reeves M, Sturm J, et al. Sex difference in long-term outcomes of stroke in the INternational STroke oUtComes sTudy (INSTRUCT): a meta-analysis of individual patient data. PROSPERO 2016:CRD42016036723. York, UK: Centre for Reviews and Dissemination, University of York; 2016 [cited 2016 12 Sep]. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036723

238. Sulter G, Steen C, Keyser JD. Use of the Barthel Index and Modified Rankin Scale in acute stroke trials. Stroke. 1999;30:1538-1541.

239. Sturm JW, Dewey HM, Donnan GA, Macdonell RAL, McNeil JJ, Thrift AG. Handicap after stroke: how does it relate to disability, perception of recovery, and stroke subtype? The North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2002;33:762-768.

240. Harwood RH, Ebrahim S. The London handicap scale. Journal of Neurology, Neurosurgery & Psychiatry. 2000;69:406-406.

241. Seaman SR, White IR, Copas AJ, Li L. Combining multiple imputation and inverse-probability weighting. Biometrics. 2012;68:129-37.

242. Gur AY, Tanne D, Bornstein NM, Milo R, Auriel E, Shopin L, et al. Stroke in the very elderly: characteristics and outcome in patients aged >/=85 years with a first-ever ischemic stroke. Neuroepidemiology. 2012;39:57-62.

243. Russo T, Felzani G, Marini C. Stroke in the very old: a systematic review of studies on incidence, outcome, and resource use. J Aging Res. 2011;2011:108785.

244. Faraji F, Ghasami K, Talaie-Zanjani A, Mohammadbeigi A. Prognostic factors in acute stroke, regarding to stroke severity by Canadian Neurological Stroke Scale: A hospital-based study. Asian Journal of Neurosurgery. 2013;8:78-82. Available from: PMC

245. Kakar P, Boos CJ, Lip GYH. Management of atrial fibrillation. Vascular Health and Risk Management. 2007;3:109-116. Available from: PMC

246. Fox J, Garber P, Hoffman M, Johnson D, Schaefer P, Vien J, et al. Morphological characteristics of skeletal muscles in relation to gender. Aging Clin Exp Res. 2003;15:264-9.

247. Paolucci S, Bragoni M, Coiro P, De Angelis D, Fusco FR, Morelli D, et al. Is sex a prognostic factor in stroke rehabilitation? A matched comparison. Stroke. 2006;37:2989-94.

248. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:e98-e169.

249. Aberg AC. Gender comparisons of function-related dependence, pain and insecurity in geriatric rehabilitation. J Rehabil Med. 2005;37:378-84.

250. Roding J, Glader EL, Malm J, Eriksson M, Lindstrom B. Perceived impaired physical and cognitive functions after stroke in men and women between 18 and 55 years of age--a national survey. Disabil Rehabil. 2009;31:1092-9.

251. Harris CR, Jenkins M, Glaser D. Gender differences in risk assessment: why do women take fewer risks than men? Judgment and Decision Making. 2006;1:48.

252. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet neurology. 2008;7:915-926. Available from: PMC

253. Obembe AO, Eng JJ. Rehabilitation interventions for improving social participation after stroke: a systematic review and meta-analysis. Neurorehabil Neural Repair. 2016;30:384-92.

254. Abdul-Rahim AH, Fulton RL, Sucharew H, Kleindorfer D, Khatri P, Broderick JP, et al. National institutes of health stroke scale item profiles as predictor of patient outcome: external validation on independent trial data. Stroke. 2015;46:395-400.

255. Kapoor A, Lanctôt KL, Bayley M, Kiss A, Herrmann N, Murray BJ, et al. “Good outcome” isn’t good enough. Stroke [10.1161/STROKEAHA.117.016728]. 2017.

256. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:1545-1588.

257. Harwood RH, Rogers A, Dickinson E, Ebrahim S. Measuring handicap: the London Handicap Scale, a new outcome measure for chronic disease. Quality in Health Care. 1994;3:11-16. Available from: PMC

258. Hammel J, Magasi S, Heinemann A, Whiteneck G, Bogner J, Rodriguez E. What does participation mean? An insider perspective from people with disabilities. Disabil Rehabil. 2008;30:1445-60.

259. Tse T, Douglas J, Lentin P, Carey L. Measuring participation after stroke: a review of frequently used tools. Arch Phys Med Rehabil. 2013;94:177-92.

260. Jenkinson C, Mant J, Carter J, Wade D, Winner S. The London handicap scale: a re-evaluation of its validity using standard scoring and simple summation. J Neurol Neurosurg Psychiatry. 2000;68:365-7.

261. Olaiya MT, Cadilhac DA, Kim J, Nelson MR, Srikanth VK, Andrew NE, et al. Long-term unmet needs and associated factors in stroke or TIA survivors: An observational study. Neurology. 2017;89:68-75.

262. Risselada R, Lingsma HF, Molyneux AJ, Kerr RS, Yarnold J, Sneade M, et al. Prediction of two month modified Rankin Scale with an ordinal prediction model in patients with aneurysmal subarachnoid haemorrhage. BMC Med Res Methodol. 2010;10:86.

263. Blizzard CL, Quinn SJ, Canary JD, Hosmer DW. Log-Link regression models for ordinal responses. Open Journal of Statistics. 2013;3:16.

264. Kwon S, Hartzema AG, Duncan PW, Min-Lai S. Disability measures in stroke: relationship among the Barthel Index, the Functional Independence Measure, and the Modified Rankin Scale. Stroke. 2004;35:918-23.

265. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, et al. Factors contributing to sex differences in functional outcomes and participation after stroke. Neurology [10.1212/WNL.0000000000005602]. 2018.

266. Ware J, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1993.

267. Anderson C, Laubscher S, Burns R. Validation of the Short Form 36 (SF-36) Health Survey Questionnaire among stroke patients. Stroke [10.1161/01.STR.27.10.1812]. 1996;27:1812.

268. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Making. 2010;30:341-54.

269. StataCorp. Stata Statistical Software: Release 12; 2011.

270. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21:271-92.

271. Norman R, Church J, van den Berg B, Goodall S. Australian health-related quality of life population norms derived from the SF-6D. Aust N Z J Public Health. 2013;37:17-23.

272. Rabin R, Oemar M, Oppe M, Janssen B, Herdman M. EQ-5D-3L user guide. Basic information on how to use the EQ-5D-5L instrument. Rotterdam: EuroQol Group. 2011;22.

273. Carod-Artal FJ. Determining quality of life in stroke survivors. Expert Review of Pharmacoeconomics & Outcomes Research. 2012;12:199-211.

274. Richardson J, Khan MA, Iezzi A, Maxwell A. Comparing and explaining differences in the magnitude, content, and sensitivity of utilities predicted by the EQ-5D, SF-6D, HUI 3, 15D, QWB, and AQoL-8D multiattribute utility instruments. Med Decis Making. 2015;35:276-91.

275. Hawthorne G, Richardson J, Day NA. A comparison of the Assessment of Quality of Life (AQoL) with four other generic utility instruments. Ann Med. 2001;33:358-70.

276. Hawthorne G, Osborne R. Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. Aust N Z J Public Health. 2005;29:136-42.

277. Kim SK, Kim SH, Jo MW, Lee SI. Estimation of minimally important differences in the EQ-5D and SF-6D indices and their utility in stroke. Health Qual Life Outcomes. 2015;13:32.

278. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. 1999.

279. Forman DE, Maurer MS, Boyd C, Brindis R, Salive ME, Horne FM, et al. Multimorbidity in older adults with cardiovascular disease. J Am Coll Cardiol. 2018;71:2149-2161.

280. Feigin VL, Norrving B, George MG, Foltz JL, Roth GA, Mensah GA. Prevention of stroke: a strategic global imperative. Nat Rev Neurol. 2016;12:501-12.

281. Besdine RW, Wetle TF. Improving health for elderly people: an international health promotion and disease prevention agenda. Aging Clinical and Experimental Research. 2010;22:219-230.

282. Bill O, Zufferey P, Faouzi M, Michel P. Severe stroke: patient profile and predictors of favorable outcome. J Thromb Haemost. 2013;11:92-9.

283. Zilli C, Brooke RI, Lau CL, Merskey H. Screening for psychiatric illness in patients with oral dysesthesia by means of the General Health Questionnaire--twenty-eight item version (GHQ-28) and the Irritability, Depression and Anxiety Scale (IDA). Oral Surg Oral Med Oral Pathol. 1989;67:384-9.

284. Lökk J, Delbari A. Management of depression in elderly stroke patients. Neuropsychiatric Disease and Treatment. 2010;6:539-549. Available from: PMC

285. Eriksson M, Asplund K, Glader EL, Norrving B, Stegmayr B, Terent A, et al. Self-reported depression and use of antidepressants after stroke: a national survey. Stroke. 2004;35:936-41.

286. Shi Y, Yang D, Zeng Y, Wu W. Risk factors for post-stroke depression: a meta-analysis. Frontiers in Aging Neuroscience. 2017;9:218. Available from: PMC

287. Zalihic A, Markotic V, Zalihic D, Mabic M. Gender and quality of life after cerebral stroke. Bosn J Basic Med Sci. 2010;10:94-9.

288. Hawthorne G, Richardson J, Day N. Using the Assessment of Quality of life (AQoL) version 1. Melbourne: Centre for Health Program Evaluation. 2001.

289. Bailey H, Kind P. Preliminary findings of an investigation into the relationship between national culture and EQ-5D value sets. Qual Life Res. 2010;19:1145-54.

290. Heikinheimo T, Chimbayo D. Quality of life after first-ever stroke: An interview-based study from Blantyre, Malawi. Malawi Med J. 2015;27:50-4.

291. Lu M, Lyden PD, Brott TG, Hamilton S, Broderick JP, Grotta JC. Beyond subgroup analysis: improving the clinical interpretation of treatment effects in stroke research. J Neurosci Methods. 2005;143:209-16.

292. Zhou J, Zhang Y, Arima H, Zhao Y, Zhao H, Zheng D, et al. Sex differences in clinical characteristics and outcomes after intracerebral haemorrhage: results from a 12-month prospective stroke registry in Nanjing, China. BMC Neurology. 2014;14:172. Available from: PMC

293. Salihovic D, Smajlovic D, Sinanovic O, Kojic B. Sex differences in patients with acute ischemic stroke in Tuzla region, Bosnia and Herzegovina. Bosn J Basic Med Sci. 2010;10:116-20.

294. Appelros P, Nydevik I, Seiger A, Terent A. Predictors of severe stroke: influence of preexisting dementia and cardiac disorders. Stroke. 2002;33:2357-62.

295. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Current Cardiology Reviews. 2010;6:150-161. Available from: PMC

296. Renoux C, Coulombe J, Li L, Ganesh A, Silver L, Rothwell PM. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. Stroke. 2017;48:2731-2738.

297. Park JM, Kang K, Cho YJ, Hong KS, Lee KB, Park TH, et al. Comparative effectiveness of prestroke aspirin on stroke severity and outcome. Ann Neurol. 2016;79:560-8.

298. Oh MS, Yu KH, Roh JK, Lee BC. Gender differences in the mortality and outcome of stroke patients in Korea. Cerebrovasc Dis. 2009;28:427-34.

299. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.

300. Strandgaard S. Cerebral blood flow in the elderly: impact of hypertension and antihypertensive treatment. Cardiovasc Drugs Ther. 1991;4 Suppl 6:1217-21.

301. Golden AG, Tewary S, Dang S, Roos BA. Care management's challenges and opportunities to reduce the rapid rehospitalization of frail community-dwelling older adults. Gerontologist. 2010;50:451-8.

302. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-56.

303. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. Journal of Leukocyte Biology. 2010;87:779-789. Available from: PMC

304. Abdul-Rahim AH, Fulton RL, Sucharew H, Kleindorfer D, Khatri P, Broderick JP, et al. National Institutes of Health Stroke Scale item profiles as predictor of patient outcome. Stroke [10.1161/STROKEAHA.114.006837]. 2015;46:395.

305. Barbieri A, Giuliani E, Carone C, Pederzoli F, Mascheroni G, Greco G, et al. Clinical severity of ischemic stroke and neural damage biomarkers in the acute setting: the STROke MArkers (STROMA) study. Minerva Anestesiol. 2013;79:750-7.

306. Desai Y, El-Chami MF, Leon AR, Merchant FM. Management of atrial fibrillation in elderly adults. J Am Geriatr Soc. 2017;65:185-193.

307. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370:2467-77.

308. Gibson CL. Cerebral ischemic stroke: is gender important? Journal of Cerebral Blood Flow & Metabolism. 2013;33:1355-1361. Available from: PMC

309. Hedna VS, Bodhit AN, Ansari S, Falchook AD, Stead L, Heilman KM, et al. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? J Clin Neurol. 2013;9:97-102.

310. Etherton MR, Wu O, Cougo P, Giese AK, Cloonan L, Fitzpatrick KM, et al. Structural integrity of normal appearing white matter and sex-specific outcomes after acute ischemic stroke. Stroke. 2017;48:3387-3389.

311. Campbell BC, Mitchell PJ, Yan B, Parsons MW, Christensen S, Churilov L, et al. A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA). Int J Stroke. 2014;9:126-32.

312. Beery AK, Zucker I. Sex Bias in Neuroscience and Biomedical Research. Neuroscience and biobehavioral reviews. 2011;35:565-572. Available from: PMC

313. Becker JB, Prendergast BJ, Liang JW. Female rats are not more variable than male rats: a meta-analysis of neuroscience studies. Biology of Sex Differences. 2016;7:34. Available from: PMC

314. McCullough LD, de Vries GJ, Miller VM, Becker JB, Sandberg K, McCarthy MM. NIH initiative to balance sex of animals in preclinical studies: generative questions to guide policy, implementation, and metrics. Biology of Sex Differences. 2014;5:15.

315. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. J Stroke. 2017;19:3-10.

316. Hsieh JT, Ang BT, Ng YP, Allen JC, King NKK. Comparison of gender differences in intracerebral hemorrhage in a multi-ethnic Asian population. PLOS ONE. 2016;11:e0152945.

317. Cadilhac D, Lannin N, Anderson C, Andrew N, Kim J, Kilkenny M, et al. The Australian Stroke Clinical Registry annual report 2013. Heidelberg: The Florey Institute of Neuroscience and Mental Health. 2015.

318. Australian Commission on Safety Quality in Health Care. Operating principles and technical standards for Australian Clinical Quality Registries. The Commission; 2008.

319. Cadilhac DA, Lannin NA, Anderson CS, Levi CR, Faux S, Price C, et al. Protocol and pilot data for establishing the Australian Stroke Clinical Registry. Int J Stroke. 2010;5:217-26.

320. Cadilhac DA, Lannin NA, Anderson CS, Andrew N, Kim J, Kilkenny M, et al. The Australian Stroke Clinical Registry annual report 2012. Australia; 2013.

321. Australian Stroke Clinical Registry. AuSCR Newsletter. Australia: AuSCR; 2014 [26/03/2015]. Available from: http://www.auscr.com.au

322. Australian Bureau of Statistics. Socio-economic indexes for areas (SEIFA). Canberra, Australia: Australian Bureau of Statistics. 2011.

323. Sim J, Teece L, Dennis MS, Roffe C. Validation and recalibration of two multivariable prognostic models for survival and independence in acute stroke. PLoS One. 2016;11:e0153527.

324. National Stroke Foundation. Clinical guidelines for stroke management 2010. Melbourne, Australia; 2010.

325. Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. Stroke. 2004;35:607-12.

326. Barker-Collo S, Bennett DA, Krishnamurthi RV, Parmar P, Feigin VL, Naghavi M, et al. Sex differences in stroke incidence, prevalence, mortality and disability-adjusted life years: results from the Global Burden of Disease Study 2013. Neuroepidemiology. 2015;45:203-214.

327. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology. A Systematic Review. 2009;40:1082-1090.

328. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. Stroke. 2002;33:1041-7.

329. Cadilhac DA, Kilkenny MF, Levi CR, Lannin NA, Thrift AG, Kim J, et al. Risk-adjusted hospital mortality rates for stroke: evidence from the Australian Stroke Clinical Registry (AuSCR). Med J Aust. 2017;206:345-350.

330. Bushnell C, Howard VJ, Lisabeth L, Caso V, Gall S, Kleindorfer D, et al. Sex differences in the evaluation and treatment of acute ischaemic stroke. Lancet Neurol. 2018;17:641-650.

331. Holloway RG, Arnold RM, Creutzfeldt CJ, Lewis EF, Lutz BJ, McCann RM, et al. Palliative and end-of-life care in stroke: A statement for healthcare professionals

from the American Heart Association/American Stroke Association. Stroke [Article]. 2014;45:1887-1916. Available from: Scopus

332. O'Connor M, Beattie J, Hong E, McKechnie R, Lee K. End-of-life care needs of people dying from stroke in Australia, New Zealand and Singapore: A space for palliative care. Asia Pacific Journal of Health Management. 2014;9:35.

333. Diener HC, Weimar C, Weber R. Antiplatelet therapy in secondary stroke prevention--state of the art. J Cell Mol Med. 2010;14:2552-60.

334. Simpson CR, Wilson C, Hannaford PC, Williams D. Evidence for age and sex differences in the secondary prevention of stroke in Scottish primary care. Stroke. 2005;36:1771-5.

335. Gallacher KI, Batty GD, McLean G, Mercer SW, Guthrie B, May CR, et al. Stroke, multimorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. BMC Medicine. 2014;12:151.

336. Shahpouri MM, Mousavi S, Khorvash F, Mousavi SM, Hoseini T. Anticoagulant therapy for ischemic stroke: a review of literature. J Res Med Sci. 2012;17:396-401.

337. Broussalis E, Kunz A, Luthringshausen G, Ladurner G, Trinka E, Killer M. Gender differences in patients with intravenous thrombolytic and conservative treatment for acute ischemic stroke. J Neurol Neurophysiol. 2011;2:117.

338. Thayabaranathan T, Andrew NE, Kilkenny MF, Stolwyk R, Thrift AG, Grimley R, et al. Factors influencing self-reported anxiety or depression following stroke or TIA using linked registry and hospital data. Qual Life Res. 2018.

339. Kilkenny M, Churilov L, Cadilhac DA. Risk-adjusted hospital mortality rates for stroke: evidence from the Australian Stroke Clinical Registry (AuSCR). The Medical Journal Of Australia. 2017;207:315-316.

340. National Stroke Foundation. National Stroke Audit – Acute Services Report 2015. Melbourne, Australia; 2015 [cited 22 May 2017]. Available from: https://informme.org.au/

341. Jamrozik K, Broadhurst RJ, Lai N, Hankey GJ, Burvill PW, Anderson CS. Trends in the incidence, severity, and short-term outcome of stroke in Perth, Western Australia. Stroke [10.1161/01.STR.30.10.2105]. 1999;30:2105.

342. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, et al. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational

STRoke oUtComes sTudy). Circulation: Cardiovascular Quality and Outcomes [10.1161/CIRCOUTCOMES.116.003436]. 2017;10.

343. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, et al. Adelaide Stroke Incidence Study. Stroke [10.1161/STROKEAHA.113.675140]. 2013.

344. Thrift AG, Dewey HM, Macdonell RAL, McNeil JJ, Donnan GA. Stroke Incidence on the East Coast of Australia. Stroke [10.1161/01.STR.31.9.2087]. 2000;31:2087.

345. National Stroke Foundation. National Stroke Audit – acute services clinical audit report 2015. Melbourne, Australia; 2015.

346. National Stroke Foundation. National Stroke Audit – acute services clinical audit report 2013. Melbourne, Australia; 2014.

347. Ganesh A, Luengo-Fernandez R, Wharton RM, Gutnikov SA, Silver LE, Mehta Z, et al. Time course of evolution of disability and cause-specific mortality after ischemic stroke: implications for trial design. J Am Heart Assoc. 2017;6.

348. Howard G, Evans GW, Murros KE, Toole JF, Lefkowitz D, Truscott BL. Cause specific mortality following cerebral infarction. J Clin Epidemiol. 1989;42:45-51.

349. Mogensen UB, Olsen TS, Andersen KK, Gerds TA. Cause-specific mortality after stroke: relation to age, sex, stroke severity, and risk factors in a 10-year follow-up study. J Stroke Cerebrovasc Dis. 2013;22:e59-65.

350. Australian Institute of Health and Welfare. About National Death Index. AIHW; 2018 [updated 20 Feb 2018; cited 2018 25 May]. https://www.aihw.gov.au/about-our-data/our-data-collections/national-death-index/about-national-death-index.

351. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke [10.1161/01.STR.24.1.35]. 1993;24:35.

352. Nichols M, Peterson K, Herbert J, Alston L, Allender S. Australian Heart Disease Statistics 2015. National Heart Foundation of Australia; 2016.

353. Australian Institute of Health and Welfare. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. AIHW; 2012 [cited 2017 1 Dec]. Available from: https://www.aihw.gov.au/reports/cancer/cancer-survival-and-prevalence-in-australia-perio/data

354. Dumurgier J, Elbaz A, Ducimetière P, Tavernier B, Alpérovitch A, Tzourio C. Slow walking speed and cardiovascular death in well functioning older adults: prospective cohort study. BMJ [10.1136/bmj.b4460]. 2009;339.

355. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute Ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke [10.1161/STR.0000000000000158]. 2018.

356. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, et al. Very early mobilization after stroke fast-tracks return to walking. Stroke [10.1161/STROKEAHA.110.594598]. 2011;42:153.

357. Kappelle LJ. Preventing deep vein thrombosis after stroke: strategies and recommendations. Current Treatment Options in Neurology. 2011;13:629-635. Available from: PMC

358. Adelborg K, Sundbøll J, Sørensen HT. Arterial cardiovascular events and mortality following venous thromboembolism. Annals of Translational Medicine. 2015;3:117. Available from: PMC

359. White AK, Thomson CS, Forman D, Meryn S. Men's health and the excess burden of cancer in men. European Urology Supplements. 2010;9:467-470.

360. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133:1104-1114. Available from: PMC

361. Soler EP, Ruiz VC. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. Current Cardiology Reviews. 2010;6:138-149. Available from: PMC

362. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2011:Cd001800.

363. Anderson L, Oldridge N, Thompson DR, Zwisler A-D, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Journal of the American College of Cardiology [10.1016/j.jacc.2015.10.044]. 2016;67:1.

364. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ [10.1136/bmj.326.7404.1419]. 2003;326:1419.

365. Lau KK, Wong YK, Teo KC, Chang RS, Hon SF, Chan KH, et al. Stroke patients with a past history of cancer are at increased risk of recurrent stroke and cardiovascular mortality. PLoS One. 2014;9:e88283.

366. Selvik HA, Bjerkreim AT, Thomassen L, Waje-Andreassen U, Naess H, Kvistad CE. When to screen ischaemic stroke patients for cancer. Cerebrovasc Dis. 2018;45:42-47.

367. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, et al. Risk of arterial thromboembolism in patients with cancer. Journal of the American College of Cardiology [10.1016/j.jacc.2017.06.047]. 2017;70:926.

368. Dearborn JL, Urrutia VC, Zeiler SR. Stroke and cancer- a complicated relationship. Journal of neurology & translational neuroscience. 2014;2:1039. Available from: PMC

369. Shigematsu K, Nakano H, Watanabe Y, Sekimoto T, Shimizu K, Nishizawa A, et al. Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan. BMJ Open. 2013;3.

370. Kelly PJ, Crispino G, Sheehan O, Kelly L, Marnane M, Merwick A, et al. Incidence, event rates, and early outcome of stroke in Dublin, Ireland: the North Dublin population stroke study. Stroke. 2012;43:2042-7.

371. Janes F, Gigli GL, D'Anna L, Cancelli I, Perelli A, Canal G, et al. Stroke incidence and 30-day and six-month case fatality rates in Udine, Italy: a population-based prospective study. Int J Stroke. 2013;8 Suppl A100:100-5.

372. Heuschmann PU, Wiedmann S, Wellwood I, Rudd A, Di Carlo A, Bejot Y, et al. Three-month stroke outcome: the European Registers of Stroke (EROS) investigators. Neurology. 2011;76:159-65.

373. Corso G, Bottacchi E, Giardini G, Di Giovanni M, Meloni T, Pesenti Campagnoni M, et al. Epidemiology of stroke in northern Italy: the Cerebrovascular Aosta Registry, 2004-2008. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2013;34:1071-1081. Available from: PubMed

374. McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. Health Qual Life Outcomes. 2016;14:133.

375. Dorman PJ, Waddell F, Slattery J, Dennis M, Sandercock P. Is the EuroQol a valid measure of health-related quality of life after stroke? Stroke. 1997;28:1876-82.

376. Viney R, Norman R, Brazier J, Cronin P, King MT, Ratcliffe J, et al. An Australian discrete choice experiment to value eq-5d health states. Health Econ. 2014;23:729-42.

377. Seaman SR, White IR, Copas AJ, Li L. Combining Multiple Imputation and Inverse-Probability Weighting. Biometrics. 2012;68:129-137. Available from: PMC

378. Simons CL, Rivero-Arias O, Yu LM, Simon J. Multiple imputation to deal with missing EQ-5D-3L data: Should we impute individual domains or the actual index? Qual Life Res. 2015;24:805-15.

379. Chang WH, Sohn MK, Lee J, Kim DY, Lee SG, Shin YI, et al. Return to work after stroke: The KOSCO Study. J Rehabil Med. 2016;48:273-9.

380. Morris R. The psychology of stroke in young adults: the roles of service provision and return to work. Stroke Research and Treatment. 2011;2011:534812. Available from: PMC

381. Becker B, McGregor AJ. Men, Women, and Pain. Gender and the Genome. 2017;1:46-50.

382. Weidner G. Why do men get more heart disease than women? An international perspective. J Am Coll Health. 2000;48:291-4.

383. Western H. Altered living: coping, hope and quality of life after stroke. British Journal of Nursing. 2007;16:1266-1270.

384. Maujean A, Davis P. The relationship between self-efficacy and well-being in stroke survivors. International Journal of Physical Medicine & Rehabilitation. 2013;1:1-10.

385. Paul SL, Sturm JW, Dewey HM, Donnan GA, Macdonell RA, Thrift AG. Long-term outcome in the North East Melbourne Stroke Incidence Study: predictors of quality of life at 5 years after stroke. Stroke. 2005;36:2082-6.

386. da Rocha NS, Schuch FB, Fleck MP. Gender differences in perception of quality of life in adults with and without chronic health conditions: the role of depressive symptoms. J Health Psychol. 2014;19:721-9.

387. Sharma K, Humane D, Shah K, Patil S, Charaniya R, Meniya J. Androgenic alopecia, premature graying, and hair thinning as independent predictors of coronary artery disease in young Asian males. Cardiovascular Endocrinology & Metabolism. 2017;6:152-158.

388. Lynch EB, Butt Z, Heinemann A, Victorson D, Nowinski CJ, Perez L, et al. A qualitative study of quality of life after stroke: the importance of social relationships. J Rehabil Med. 2008;40:518-23.

389. Carr AJ, Higginson IJ. Are quality of life measures patient centred? Bmj. 2001;322:1357-60.

390. Blauwet LA, Redberg RF. The role of sex-specific results reporting in cardiovascular disease. Cardiol Rev. 2007;15:275-8.

391. Byles JE. A thorough going over: evidence for health assessments for older persons. Aust N Z J Public Health. 2000;24:117-23.

392. Hamirudin AH, Ghosh A, Charlton K, Bonney A, Walton K. Trends in uptake of the 75+ health assessment in Australia: a decade of evaluation. Aust J Prim Health. 2015;21:423-8.

393. Byles JE, Young AF, Wheway VL. Annual health assessments for older Australian women: uptake and equity. Aust N Z J Public Health. 2007;31:170-3.

394. Dolja-Gore X, Tavener M, Majeed T, Nair BR, Byles JE. Uptake, prevalence and predictors of first-time use for the 75+ Health Assessment Scheme. Aust J Prim Health. 2017;23:476-481.

395. Ploeg J, Feightner J, Hutchison B, Patterson C, Sigouin C, Gauld M. Effectiveness of preventive primary care outreach interventions aimed at older people: meta-analysis of randomized controlled trials. Canadian Family Physician. 2005;51:1244.

396. Kursun M. RE: Balloon test occlusion, device selection, and extracorporeal membrane oxygenation in the transcatheter closure of coronary artery fistula. Anatolian Journal of Cardiology. 2015;15:1034-1035.

397. Australian Institute of Health and Welfare. In: Prevention of cardiovascular disease, diabetes and chronic kidney disease: targeting risk factors. 2009. Canberra: AIHW. Cat. No. PHE 118.

398. Si S. Evaluations of the 45-49 year old health check program in Australian general practice (Doctoral dissertation). [Adelaide]: University of Adelaide; 2014.

399. Teo CH, Ng CJ, Booth A, White A. Barriers and facilitators to health screening in men: A systematic review. Soc Sci Med. 2016;165:168-176.

400. Kelly S, Martin S, Kuhn I, Cowan A, Brayne C, Lafortune L. Barriers and facilitators to the uptake and maintenance of healthy behaviours by people at mid-life: a rapid systematic review. PLoS One. 2016;11:e0145074.

401. Deng YX, Wang YL, Gao BQ, Wang CX, Zhao XQ, Liu LP, et al. Age differences in clinical characteristics, health care, and outcomes after ischemic stroke in China. CNS Neurosci Ther. 2012;18:819-26.

402. Zeevi N, Chhabra J, Silverman IE, Lee NS, McCullough LD. Acute stroke management in the elderly. Cerebrovasc Dis. 2007;23:304-8.

403. Gaynor EJ, Geoghegan SE, O'Neill D. Ageism in stroke rehabilitation studies. Age Ageing. 2014;43:429-31.

404. Duckett S. Expanding the breadth of Medicare: learning from Australia. Health Econ Policy Law. 2018;13:344-368.

405. Australian Bureau of Statistics. Patient experiences in Australia: summary of findings, 2015–16. Canberra: ABS; 2016.

406. Bushnell CD, Colon-Emeric CS. Secondary stroke prevention strategies for the oldest patients: possibilities and challenges. Drugs Aging. 2009;26:209-30.

407. Black-Schaffer RM, Winston C. Age and functional outcome after stroke. Top Stroke Rehabil. 2004;11:23-32.

408. Bagg S, Pombo AP, Hopman W. Effect of age on functional outcomes after stroke rehabilitation. Stroke. 2002;33:179-85.

409. Nobili A, Garattini S, Mannucci PM. Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. Journal of Comorbidity; Vol 1, No 1 (2011): Inaugural Issue. 2011.

410. Resar R, Griffin F, Haraden C, Nolan T. In: Using care bundles to improve health care quality. IHI innovation series white paper. Cambridge, MA: Institute for Healthcare Improvement; 2012. 2014

411. Burton CR, Payne S. Integrating palliative care within acute stroke services: developing a programme theory of patient and family needs, preferences and staff perspectives. BMC Palliative Care. 2012;11:22-22. Available from: PMC

412. Haque S, Reeves MJ, Sucharew H, Alwell KA, Moomaw CJ, Woo D, et al. The Frailty Index: a novel predictor of stroke outcomes. Stroke. 2012;43:A30.

413. Liu M, Li G, Tang J, Liao Y, Li L, Zheng Y, et al. The influence of sex in stroke thrombolysis: a systematic review and meta-analysis. Journal of Clinical Neurology (Seoul, Korea). 2018;14:141-152. Available from: PMC

414. Carvalho A, Cunha A, Gregório T, Paredes L, Costa H, Veloso M, et al. Is the efficacy of endovascular treatment for acute ischemic stroke sex-related. Interventional Neurology. 2018;7:42-47.

415. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet. 2014;383:1973-80.

416. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, et al. Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): A Meta-Analysis of Individual Participant Data. Circ Cardiovasc Qual Outcomes. 2017;10.

417. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nat Rev Cardiol. 2016.

418. Gillis AM. Atrial fibrillation and ventricular arrhythmias. Circulation [10.1161/CIRCULATIONAHA.116.025312]. 2017;135:593.

419. Ko D, Rahman F, Martins MAP, Hylek EM, Ellinor PT, Schnabel RB, et al. Atrial fibrillation in women: treatment. Nature Reviews Cardiology [Review Article]. 2016;14:113.

420. Huang JH, Yang HY, Hsu CY, Lin YK, Chen SA, Chen YJ. Gender differences in trend of hospital management for atrial fibrillation: a nationwide population-based analysis. Int J Cardiol. 2011;153:89-94.

421. Suárez Fernández C, Formiga F, Camafort M, Cepeda Rodrigo JM, Díez-Manglano J, Pose Reino A, et al. Antithrombotic treatment in elderly patients with atrial fibrillation: a practical approach. BMC Cardiovascular Disorders. 2015;15:143. Available from: PMC

422. Jankowska-Polańska B, Katarzyna L, Lidia A, Joanna J, Dudek K, Izabella U. Cognitive function and adherence to anticoagulation treatment in patients with atrial fibrillation. Journal of Geriatric Cardiology : JGC. 2016;13:559-565. Available from: PMC

423. Coyle D, Coyle K, Cameron C, Lee K, Kelly S, Steiner S, et al. Cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. Value Health. 2013;16:498-506.

424. Kim J, Andrew NE, Thrift AG, Bernhardt J, Lindley RI, Cadilhac DA. The potential health and economic impact of improving stroke care standards for Australia Int J Stroke. 2017:1-11.

425. Cadilhac DA, Andrew NE, Kilkenny MF, Hill K, Grabsch B, Lannin NA, et al. Improving quality and outcomes of stroke care in hospitals: Protocol and statistical analysis plan for the Stroke123 implementation study. Int J Stroke. 2018;13:96-106.

426. Cadilhac DA, Andrew NE, Stroil Salama E, Hill K, Middleton S, Horton E, et al. Improving discharge care: the potential of a new organisational intervention to improve discharge after hospitalisation for acute stroke, a controlled before-after pilot study. BMJ Open. 2017;7:e016010.

427. Middleton S, Lydtin A, Comerford D, Cadilhac DA, McElduff P, Dale S, et al. From QASC to QASCIP: successful Australian translational scale-up and spread of a proven intervention in acute stroke using a prospective pre-test/post-test study design. BMJ Open. 2016;6:e011568.

428. Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. The Lancet. 2011;378 1699-1706.

429. Ormseth CH, Sheth KN, Saver JL, Fonarow GC, Schwamm LH. The American Heart Association's Get With the Guidelines (GWTG)-Stroke development and impact on stroke care. Stroke and Vascular Neurology [10.1136/svn-2017-000092]. 2017.

430. Sun Y, Paulus D, Eyssen M, Maervoet J, Saka O. A systematic review and meta-analysis of acute stroke unit care: what's beyond the statistical significance? BMC Med Res Methodol. 2013;13:132.

431. Emberson J, Whincup P, Morris R, Walker M, Ebrahim S. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. Eur Heart J. 2004;25:484-91.

432. Feigin VL, Norrving B, Mensah GA. Primary prevention of cardiovascular disease through population-wide motivational strategies: insights from using smartphones in stroke prevention. BMJ Global Health. 2017;2:e000306. Available from: PMC

433. Jackson H, Shiell A. Preventive health: how much does Australia spend and is it enough. Foundation for Alcohol Research and Education, Canberra. 2017.

434. Jennum P, Iversen HK, Ibsen R, Kjellberg J. Cost of stroke: a controlled national study evaluating societal effects on patients and their partners. BMC health services research. 2015;15:466-466.

435. Lopez-Bastida J, Oliva Moreno J, Worbes Cerezo M, Perestelo Perez L, Serrano-Aguilar P, Montón-Álvarez F. Social and economic costs and health-related

quality of life in stroke survivors in the Canary Islands, Spain. BMC health services research. 2012;12:315-315.

436. Lynch EA, Cadilhac DA, Luker JA, Hillier SL. Inequities in access to inpatient rehabilitation after stroke: an international scoping review. Top Stroke Rehabil. 2017;24:619-626.

437. Hung Y-X, Huang P-C, Chen K-T, Chu W-C. What do stroke patients look for in game-based rehabilitation: a survey study. Medicine. 2016;95:e3032. Available from: PMC

438. Chumbler NR, Quigley P, Li X, Morey M, Rose D, Sanford J, et al. Effects of telerehabilitation on physical function and disability for stroke patients. Stroke [10.1161/STROKEAHA.111.646943]. 2012;43:2168.

439. Lynch EA, Luker JA, Cadilhac DA, Hillier SL. Inequities in access to rehabilitation: exploring how acute stroke unit clinicians decide who to refer to rehabilitation. Disabil Rehabil. 2016;38:1415-24.

440. Kongkasuwan R, Voraakhom K, Pisolayabutra P, Maneechai P, Boonin J, Kuptniratsaikul V. Creative art therapy to enhance rehabilitation for stroke patients: a randomized controlled trial. Clin Rehabil. 2016;30:1016-1023.

441. Kersten P, Low JT, Ashburn A, George SL, McLellan DL. The unmet needs of young people who have had a stroke: results of a national UK survey. Disabil Rehabil. 2002;24:860-6.

442. Ullberg T, Zia E, Petersson J, Norrving B. Perceived unmet rehabilitation needs 1 year after stroke: an observational study from the Swedish Stroke Register. Stroke. 2016;47:539-41.

443. McKevitt C, Fudge N, Redfern J, Sheldenkar A, Crichton S, Rudd AR, et al. Self-reported long-term needs after stroke. Stroke. 2011;42:1398-403.

444. Röding J, Glader E-L, Malm J, Lindström B. Life satisfaction in younger individuals after stroke: different predisposing factors among men and women. Journal of Rehabilitation Medicine. 2010;42:155-161.

445. Andrew NE, Kilkenny MF, Lannin NA, Cadilhac DA. Is health-related quality of life between 90 and 180 days following stroke associated with long-term unmet needs? Qual Life Res. 2016;25:2053-62.

446. Stroke Foundation. EnableMe: Helping you with your own stroke recovery. Melbourne, Australia: Stroke Foundation; 2018 [cited 2018 16 July]. Available from: https://enableme.org.au/

447. Jha P. Reliable direct measurement of causes of death in low- and middle-income countries. BMC Medicine. 2014;12:19-19. Available from: PMC

448. Putaala J. Ischemic stroke in the young: current perspectives on incidence, risk factors, and cardiovascular prognosis. European Stroke Journal. 2016;1:28-40.

449. National Stroke Foundation. Clinical guidelines for stroke management 2017. Melbourne, Australia; 2017.

450. Baatiema L, de-Graft Aikins A, Sav A, Mnatzaganian G, Chan CKY, Somerset S. Barriers to evidence-based acute stroke care in Ghana: a qualitative study on the perspectives of stroke care professionals. BMJ Open [10.1136/bmjopen-2016-015385]. 2017;7.

451. Sposato LA, Esnaola MM, Zamora R, Zurru MC, Fustinoni O, Saposnik G. Quality of ischemic stroke care in emerging countries: the Argentinian National Stroke Registry (ReNACer). Stroke. 2008;39:3036-41.

452. Pandian JD, William AG, Kate MP, Norrving B, Mensah GA, Davis S, et al. Strategies to improve stroke care services in low- and middle-income countries: a systematic review. Neuroepidemiology. 2017;49:45-61.

453. Charmes J. Time use across the world: findings of a world compilation of time-use surveys. New York, USA: United Nations Development Programme.; 2015 [cited 2018 08 June]. Available from: http://hdr.undp.org/sites/default/files/charmes_hdr_2015_final.pdf

454. Bruno A, Switzer JA, Durkalski VL, Nichols FT. Is a prestroke modified Rankin Scale sensible? Int J Stroke. 2011;6:414-5.

455. Fearon P, McArthur KS, Garrity K, Graham LJ, McGroarty G, Vincent S, et al. Prestroke Modified Rankin Stroke Scale has moderate interobserver reliability and validity in an acute stroke setting. Stroke [10.1161/STROKEAHA.112.670422]. 2012;43:3184.

456. Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. Neurology. 2013;81:1588-95.

457. Tran PL, Leigh Blizzard C, Srikanth V, Hanh VT, Lien NT, Thang NH, et al. Health-related quality of life after stroke: reliability and validity of the Duke Health Profile for use in Vietnam. Qual Life Res. 2015;24:2807-14.

458. Nguyen LH, Tran BX, Hoang Le QN, Tran TT, Latkin CA. Quality of life profile of general Vietnamese population using EQ-5D-5L. Health and Quality of Life Outcomes. 2017;15:199.

459. Kwon S, Park J-H, Kim W-S, Han K, Lee Y, Paik N-J. Health-related quality of life and related factors in stroke survivors: Data from Korea National Health and Nutrition Examination Survey (KNHANES) 2008 to 2014. PLOS ONE. 2018;13:e0195713.